Long-Term Adherence to Direct Oral Anticoagulants in Patients with Atrial Fibrillation: A Comparative Cross-Sectional Study

Anouk J.W. Gulpen, Dionne C.W. Braeken, Simon Schalla, Hugo Ten Cate, Harry J. Crijns, Arina J. Ten Cate-Hoek

Keywords
Direct oral anticoagulants · Thrombosis · Adherence

Abstract
Background: Long-term treatment with direct oral anticoagulants (DOAC) is required for the majority of patients with nonvalvular atrial fibrillation (AF) to prevent ischemic stroke and systemic embolism. Adherence to therapy may impact clinical outcomes. Therefore, the purpose of this study was to assess the potential impact of structured follow-up on long-term adherence to DOAC therapy compared to standard care.

Methods: This is a cross sectional study on the implementation phase of medication adherence to DOACs, comparing patients with AF following completion of structured follow-up of minimally 1 year with those who received standard care. All patients used DOACs for more than 2 years and completed a questionnaire on adherence. Adherence was measured with the Morisky Medication Adherence Scale-8 (MMAS-8) score and assessed via an online web portal.

Results: A total of 212 patients were included. The mean MMAS-8 score was 7.55 (SD 0.93) after structured follow-up and 7.25 (SD 1.01) for standard care; \( p = 0.045 \). Following structured follow-up 64.1% of patients had a high adherence (MMAS score of 8) compared to 50% receiving standard care; \( p = 0.05 \). Patients following structured follow-up on a once daily DOAC regime had higher MMAS-8 scores compared to those on a twice daily regime; 7.74 (SD 0.74) versus 7.00 (SD 1.22); \( p < 0.001 \). The rates of minor bleedings were 10.6% versus 21.4% respectively, \( p = 0.038 \).

Conclusion: In patients on long-term DOAC treatment, adherence to therapy was significantly increased after receiving an initial period of structured follow-up compared to standard care. Additionally, adherence to DOAC therapy was higher with once-daily treatment regimen. Significant more minor bleedings were reported in the standard care group. These results indicate that implementation of structured follow-up of patients with AF using DOACs merits further evaluation.

Trial registration: METC azM/UM: 2019-1213.
Introduction

Direct oral anticoagulants (DOACs) have become the mainstay of treatment for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), since major clinical trials showed non-inferiority of DOACs as compared to vitamin K antagonists (VKA) [1–4]. DOACs include the direct Xa inhibitors rivaroxaban, apixaban, and edoxaban and the direct thrombin inhibitor dabigatran. The main advantage of DOACs compared to VKA is the use of fixed doses and thereby the absent need for routine coagulation monitoring. However, this lack of regular patient contact, an essential element of the care for patients using VKA, might result in lower treatment motivation and persistence. Consequently, adherence to medication may be diminished which, in combination with the relatively short half-life of DOACs, could increase the risk of thromboembolic complications, bleedings in case of double intake of medication following missed doses, or even all-cause mortality [5]. While the major DOAC trials showed high adherence rates to medication [6, 7], which may in part be attributable to patient selection, intensive follow-up and pill counts, data from observational cohort studies showed premature discontinuation of DOAC use in up to 25% of patients [8]. In contrast, high adherence rates were found during a 1-year structured follow-up in VKA-experienced patients that had been switched to DOACs [9]. A possible explanation for the relatively high adherence in the latter study could be the fact that these patients had already been used to structured follow-up during their prior VKA use, possibly still affecting drug intake behavior. This finding was corroborated by another study where medication adherence with DOACs was lower in anticoagulation-naïve patients compared to anticoagulation-experienced patients; however, even the latter patients showed a decline in medication adherence over time [10].

The objective of the current study was to assess the potential impact of a structured follow-up on medication adherence during the implementation phase of DOAC therapy compared to standard care. In addition, we aimed to assess the association of structured follow-up with clinical outcomes, in particular bleeding events.

Methods

Patients

This comparative cross-sectional study was conducted at a single Dutch university hospital. All patients were diagnosed with AF and taking DOACs [11] for at least 2 years. Patients who had participated in a previous cohort study with structured DOAC follow-up were asked to complete an additional online questionnaire on long-term adherence [9]. In this previous follow-up study, patients were assessed within 1 month after start of DOAC therapy and at 3, 6, and 12 months thereafter [9]. This included assessment of medication adherence and retrieval of information on bleeding or, less likely given the small sample, thrombotic events. These patients are further presented as “structured follow-up.” Figure 1 shows detailed information about the structured follow-up.

Controls were patients receiving standard care recruited from the cardiology outpatient clinic between May 1, 2019, and October 1, 2020. While visiting the outpatient clinic, patients were informed about the study. If informed consent was obtained, both patients that received structured follow-up and control patients completed the adherence questionnaire via an online web portal. The control group is further presented as “standard care.” All patients administered the adherence assessment after a DOAC treatment time of minimal 2 years.

Assessment of Medication Adherence

Adherence has been defined in accordance with adherence guidelines as the extent to which patients conform to the medication use recommendations specified by the prescriber and consists of three phases: initiation, implementation, and persistence [11]. Initiation and persistence can be reported as percentage of patients who started or stopped a treatment. In this study, we specifically assessed the

| Time points       | Structured follow-up                                                                 |
|-------------------|-------------------------------------------------------------------------------------|
| Start of DOAC therapy | Laboratory assessment of renal function                                              |
| 1 month after start | Visit to the anticoagulation clinic with assessment of □ MMAS-8 □ Assessment bleeding or thromboembolic events □ Assessment of side-effects |
| 3 months after start | Visit to the anticoagulation clinic with □ MMAS-8 □ Assessment bleeding or thromboembolic events □ Assessment of possible side-effects |
| 6 months after start | Visit to the anticoagulation clinic with □ MMAS-8 □ Assessment bleeding or thromboembolic events □ Assessment of possible side-effects □ Laboratory assessment of renal function |
| 12 months after start | Visit to the anticoagulation clinic with □ MMAS-8 □ Assessment bleeding or thromboembolic events □ Assessment of possible side-effects □ Laboratory assessment of renal function |

Fig. 1. Structured follow-up details.
implementation phase of adherence and describe the extent to which patients take their medication using the Morisky Medication Adherence Scale-8 (MMAS-8), developed by Morisky et al. [12–14]. The first seven items are yes/no-responses and the last item is a 5-point Likert scale. This last item consists of a score between zero and one in 0.25-point increments on a 5-point scale assessing how frequent patients forgot to take medications (never = 1, once- in- a-while = 0.75, sometimes = 0.5, usually = 0.25, and all the time = 0). According to the validated MMAS-8 instructions, adherence is categorized as high adherence (a score of 8), medium adherence (a score of 6 to <8), and low adherence (a score of <6). Nonadherence is further classified in intentional and nonintentional. Intentional refers to nonadherence that is deliberate and largely associated with patient motivation and is based on an active decision not to take the medication. For example: “you felt worse when you took it,” or “you felt hassled about sticking to your anticoagulation treatment plan.” Unintentional is nonadherence that is largely driven by a lack of capacity or resources to take the medication [15].

Assessment of Bleeding and Thromboembolic Events

Information on bleeding and thromboembolic events was assessed. Bleeding was defined according to the Dutch Thrombosis Service guidelines which are based on the ISTH-bleeding criteria [16]. Defining major bleeding as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intracranial, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells. Minor bleeding is defined as any bleeding that leads to a face-to-face evaluation [16]. Thromboembolic events were defined as venous thromboembolism (VTE; deep venous thrombosis or pulmonary embolism) or ischemic cerebrovascular accident (stroke) or transient ischemic attack.

Ethics

The study complies with the principles and requirements of the Declaration of Helsinki and was approved by the Institutional Review Board of the Maastricht University Medical Centre+ (MUMC+) (METC azM/UM: 2019-1213). All patients provided written informed consent.

Statistical Analysis

Descriptive analyses were performed to assess baseline characteristics; continuous variables were described as medians with their associated interquartile ranges. Categorical variables were expressed as numbers and percentages. Differences in baseline characteristics were compared using the Wilcoxon-Mann-Whitney test for continuous variables and the Pearson’s χ² test for categorical variables.

For the primary outcome, the difference in mean adherence (using the MMAS-8 score) between patients following structured follow-up and standard care, as well as whether this difference was intentional or nonintentional, the student t test was used. The Pearson’s χ² test was used to assess the levels of adherence to therapy (low, medium or high), the proportion of thromboembolic events, and bleeding.

The associations between patient characteristics (sex, age, once/twice daily medication regimen, follow-up time, comedication, number of comedications a day, and history of VKA use) and adherence were tested using logistic regression. All variables with a p value <0.2 in the bivariate analyses were entered into the multivariable logistic regression model with backward variable selection, until all remaining variables were statistically significant. Variables were also checked for interactions. For all analyses, a p value of ≤0.05 was considered statistically significant. All statistical analyses were carried out using the IBM® SPSS® Statistics version 23.

Outcomes

The primary outcome of this study was the difference in adherence rate measured by the MMAS-8 scale between patients following structured follow-up and patients receiving standard care. In addition, the association between adherence with thrombotic events and bleeding complications was assessed.

Results

Patient Characteristics

From May 2019 to October 2020, a total of 212 patients were recruited: 142 patients with previous structured follow-up (median age 75 [70–80]) and 70 patients receiving standard care (median age 69 [63.5–72.0]). Baseline characteristics for patients following structured follow-up and patients receiving standard care are shown in Table 1. The average duration of DOAC use was 45 (24–70) months in the structured follow-up group versus 29 (24–40) months in the standard care group (p = 0.126); 79% of patients in the structured follow-up group were previous VKA users compared to 32.9% receiving standard care (p = <0.001). Patients were often using three or more comedications; 62% of patients versus 61.4% in both groups. Four different DOACS were prescribed with rivaroxaban 20 mg being the most prevalent in both groups: 42.6% and 41.4%, respectively.

Adherence of Patients to Therapy

Table 2 shows the results for the adherence scores of both groups. The total MMAS-8 score for the structured follow-up was (7.55 [0.93]) and (7.25 [1.01]) standard care group (p = 0.045). For the distribution of intentional and nonintentional nonadherence, there was no difference between the groups. Low adherence was similar in both groups. In the structured follow-up group, 12.0% of the patients showed a low adherence score (<6), while standard care patients showed low adherence in 17.1% (p = 0.303). In contrast, high adherence was more prevalent in the structured follow-up group where the majority of patients (64.1%) showed a high adherence score of 8, compared to 50.0% in the standard care group (p = 0.05).

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Table 3 shows the adherence score for all patients using a once daily regimen (rivaroxaban or edoxaban) compared to patients using a twice daily treatment regimen (dabigatran or apixaban). The mean MMAS-8 score was significantly different and in favor of once daily treatment; 7.15 (1.08) versus 7.61 (0.86), \( p < 0.0018 \). In the twice daily regime, 39.3% of patients showed a high adherence score while, in the once daily treatment regimen 71.7% of patients showed a high adherence score (\( p < 0.001 \)).

**Table 1. Baseline characteristics of patients**

|                         | Structured follow-up (\( N = 142 \)) | Standard care (\( N = 70 \)) | \( p \) value |
|-------------------------|--------------------------------------|-------------------------------|---------------|
| Age, median (IQR)       | 75 (70–80)                           | 69 (63.5–72.0)               | <0.001        |
| Male sex, n (%)         | 103 (74.1)                           | 51 (72.9)                    | 0.847         |
| DOAC, n (%)             |                                      |                               |               |
| Dabigatran 150 mg       | 22 (15.6)                            | 7 (10.0)                     |               |
| Dabigatran 110 mg       | 11 (7.8)                             | 4 (3.3)                      |               |
| Rivaroxaban 20 mg       | 60 (42.6)                            | 29 (41.4)                    |               |
| Rivaroxaban 15 mg       | 10 (7.1)                             | 1 (1.4)                      |               |
| Apixaban 5 mg           | 19 (13.5)                            | 18 (25.7)                    |               |
| Apixaban 2.5 mg         | 4 (2.8)                              | 4 (5.7)                      |               |
| Edoxaban 60 mg          | 11 (7.8)                             | 6 (8.6)                      |               |
| Edoxaban 30 mg          | 2 (1.4)                              | 2 (2.9)                      |               |
| Average treatment duration months, median (IQR) | 45 (24–70) | 29 (24–40) | 0.126 |
| Comedication, n (%)     |                                      |                               |               |
| <3                      | 17.6                                 | 14.3                         |               |
| 3                       | 20.4                                 | 24.3                         |               |
| >3                      | 62                                   | 61.4                         |               |
| Comedication times per day, n (%) |                                      |                               |               |
| 1                       | 21.5                                 | 22.9                         |               |
| 2                       | 65.4                                 | 57.1                         |               |
| 3                       | 12.1                                 | 17.1                         |               |
| >3                      | 0.9                                  | 2.9                          |               |
| History VKA use, n (%)  | 109 (79)                             | 23 (32.9)                    | <0.001        |

Data are mean (interquartile range) or n (%).

Table 2. Adherence of patients to DOAC therapy

|                         | Structured follow-up (\( N = 142 \)) | Standard care (\( N = 70 \)) | \( p \) value |
|-------------------------|--------------------------------------|-------------------------------|---------------|
| MMAS-8 score            | 7.55 (0.93)                          | 7.25 (1.01)                  | 0.045         |
| Intentional             | 3.78 (0.55)                          | 3.67 (0.53)                  | 0.173         |
| Nonintentional          | 3.67 (0.61)                          | 3.58 (0.60)                  | 0.278         |
| Adherence rating, n (%) |                                      |                               |               |
| Low adherence (score <6) | 17 (12.0)                            | 12 (17.1)                    | 0.303         |
| Medium adherence (score 6–8) | 34 (23.9)                        | 23 (32.9)                    | 0.072         |
| High adherence (score = 8) | 91 (64.1)                           | 35 (50.0)                    | 0.050         |

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**Table 2. Adherence of patients to DOAC therapy**

**Patient Characteristics Associated with Adherence**

Several possible confounders were assessed. The variables gender, structured follow-up, duration of the
DOAC therapy, previous use of VKA, age, and number of comediations reached a $p = \text{value of } <0.2$. In the multivariable analysis, none of the variables were significantly associated with the outcome adherence. The analysis showed an interaction between structured follow-up and once or twice daily medication use OR 10.2 ($p = 0.025$).

### Reported Events

There were no major bleedings reported in the structured follow-up group while for standard care one major bleeding was reported ($p = 0.109$). Additionally, in each group 15 minor bleedings were reported: 10.6% versus 21.4%, respectively, OR 0.43 (95% CI 0.2–0.95) $p = 0.038$. The structured follow-up group showed 2 ischemic strokes during treatment, while no ischemic events were reported in the group with standard care ($p = 0.552$).

Table 4 shows the distribution of minor bleedings. There were 30 minor bleedings in total: 8/29 (27%) patients with a low adherence score experienced a bleeding event, as compared to 14/126 (11%) patients in the high adherence group. There were significantly more minor bleedings ($p = 0.025$) in the low adherence group compared to the medium and high adherence group.

### Discussion

The main finding of this comparative cross-sectional study on the implementation phase of adherence was that the adherence to DOAC treatments was significantly increased in patients following structured follow-up compared to those receiving standard care. Almost 65% of the patients following structured follow-up had a MMAS score of 8 and were thus categorized as being highly adherent to anticoagulation therapy versus 50% of patients receiving standard care. Our current findings confirm and extend data previously reported by our group, where we showed that adherence to anticoagulation therapy within 1 year after start of DOAC treatment was reasonably good with MMAS scores of 6–8 (medium adherence) in 92% and MMAS scores of 8 (good adherence) in 8% of patients with structured follow-up [9].

Adherence to DOAC therapy has been previously studied for various patient groups with different results [17, 18]. Recently, a systematic review in AF patients showed poor clinical outcomes in nonadherent patients and a retrospective cohort study demonstrated the impact of reduced adherence to DOAC for thrombotic outcomes in patients with VTE; although adherence was overall good in 305 patients with VTE, there was an excess in recurrent VTE in the patients with a lower adherence score [19, 20]. Further, it is known that adherence declines most steeply after 3–6 months after initial prescription and declines further over time.

We did not find an impact of adherence on the occurrence of stroke or of major bleeding events in our current

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**Table 3. Adherence rates in different dosing regimes**

|                        | Once daily medication (N = 123) | Twice daily medication (N = 89) | p value |
|------------------------|---------------------------------|---------------------------------|---------|
| MMAS-8 score, mean (SD)| 7.61 (0.86)                     | 7.15 (1.08)                     | 0.008   |
| Adherence rating, N (%)|                                 |                                 |         |
| Low adherence (<6)     | 10 (8.1)                        | 19 (21.3)                       | 0.009   |
| Medium adherence (6–8) | 24 (19.5)                       | 35 (39.3)                       | 0.002   |
| High adherence (8)     | 89 (71.7)                       | 35 (39.3)                       | <0.001  |

Use of the "MMAS is protected by US Copyright laws. Permission for use is required. A license agreement is available from MMAS Research LLC 14725 NE 20th St. Bellevue WA 98007 or from dmorisky@gmail.com. Data are mean (SD) or N (%). Once daily medication: rivaroxaban, edoxaban. Twice daily medication: dabigatran, apixaban.

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**Table 4. Adherence rates related to minor bleeding frequency**

| Adherence | Minor bleedings (N = 30) | p value |
|-----------|--------------------------|---------|
| Low (N = 29) | 8                        | 0.025   |
| Medium (N = 57) | 8                        | 0.775   |
| High (N = 126) | 14                       | 0.124   |
study, due to a very low rate of these clinical outcomes in this sample. However, we did show that structured follow-up was associated with an reduced risk of minor bleeding events. A possible explanation could be that patients in the standard group may have had more comorbidities and bleeding risk factors, thus exposing them to a higher bleeding risk. Patients who have experienced bleeding could be expected to be less adherent. Therefore, the low adherence may be a result of nuisance bleeding and not vice versa.

Additionally, we found varying adherence scores for the different DOACs, with significantly better adherence scores in patients using a once-daily dosing regimen of either rivaroxaban or edoxaban, confirming previous observations from other studies [18, 21, 22]. Although one study did not find increased adherence among users of once-daily regimen [23], once-daily dosing may be an important tool for maintaining optimum anticoagulation. In our study, we found a strong interaction between structural follow-up and once-daily regimen in relation to adherence, suggesting that the successful outcomes of structural follow-up might be in part explained by the use of once-daily regimen. As adherence to DOACs is important for treatment success, prescribers should be aware of the potential implications of frequency of DOAC intake in relation to efficacy and safety of these agents. Particularly, as there seems not to be a difference in terms of efficacy and safety for once or twice-daily regimens [24].

The main limitation of this study was its small sample size which likely explains the lack of power to link adherence to major clinical outcomes with low incidence such as stroke or major bleeding. Second, almost 80% of the patients in the structured follow-up group were previously taking VKA (79% compared to 33% in standard care), this might have introduced selection bias as these patients are more likely to have higher adherence rates [10]. Third, the patient’s self-selection for the structured follow in this study may have induced further bias. Finally, our study focused on the implementation phase of adherence only and used the MMAS-8 scale as a single measure of adherence. This method is limited in the sense that it does not document actual intake of the medication and it is self-reported. The MMAS-8 only captures a few reasons or factors associated with nonadherence making it difficult to develop interventions targeting factors associated with nonadherence [25].

With continued increasing DOAC treatment rates in an ageing population, new efforts with focus on improvement of treatment adherence, concordant with guideline recommendations may help to optimize treatment. The European Heart Rhythm Association Practical Guide to DOACs provides a framework for structured initiation and follow-up for patients receiving DOACs [26]. We showed that regular scheduled contact with healthcare professionals during at least 1 year may indeed improve long term adherence to DOACs and reduce the incidence of adverse events. Yet, to our knowledge, the practical guides for DOAC follow-up have not been widely embedded in clinical practice.

Ideally, the initial prescriber (or a member of the team) would be responsible for initial patient education [26, 27]. The long-term management could practically be efficiently handled by centralized anticoagulation clinics [28, 29]. As an alternative, general practitioners or specialized nurses could also take responsibility. The recent ALL-IN trial provides a striking example of the potential gain of integrated anticoagulant care in patients with AF, showing even a 45% reduction in all-cause mortality in association with this approach, as compared to standard care [30]. Currently, also the role of mobile health in managing AF patients is investigated. Such mobile health infrastructures may be well suited within centralized anticoagulation clinics [31]. Further research is needed to evaluate how structured follow-up of patients with AF using DOACs should be performed.

**Conclusion**

In patients with AF, long-term adherence to DOAC therapy was significantly higher if a structured follow-up program was offered in comparison to standard care, which may in part be explained by the use of once-daily medication. Structured follow-up was associated with less minor bleedings. No differences were observed for major bleeding or stroke due to the low overall occurrence of these events. Our findings indicate that implementation of structured follow-up of patients with AF using DOACs merits further evaluation.

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Statement of Ethics

The study complies with the principles and requirements of the Declaration of Helsinki and was approved by the Institutional Review Board of the Maastricht University Medical Centre+ (MUMC+) (METC azM/UM: 2019-1213). All patients provided written informed consent.

Conflict of Interest Statement

H.T.C. received research funding from Bayer and Pfizer, unrelated to this work. The other authors do not report any relevant conflicts.

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