

## Adherence to oral anticoagulation in ischemic stroke patients with atrial fibrillation

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### ABSTRACT

**Background:** Non-vitamin K antagonist oral anticoagulants (NOAC) have superior safety and comparable efficacy profile compared to vitamin-K antagonists (VKAs), with more convenient dosing schemes. However, issues with adherence to the NOACs remain unsolved.

**Aims:** We sought to investigate the adherence to oral anticoagulation (OAC) and baseline factors associated with poor adherence after ischaemic stroke in patients with atrial fibrillation (AF).

**Methods:** We recruited hospitalised patients (2013–2019) from two prospective stroke registries in Larissa and Helsinki University Hospitals and invited survived patients to participate in a telephone interview. We assessed adherence with the Adherence to Refills and Medications Scale (ARMS) and defined poor adherence as a score of over 17. In addition to demographics, individual comorbidities, and stroke features, we assessed the association of CHA<sub>2</sub>DS<sub>2</sub>-VASc and SAME-TT<sub>2</sub>R<sub>2</sub> scores with poor adherence.

**Results:** Among 396 patients (median age 75.0 years, interquartile range [IQR] 70–80; 57% men; median time from ischaemic stroke to interview 21 months [IQR 12–33]; median ARMS score 17 [IQR 17–19]), 56% of warfarin users and 44% of NOAC users reported poor adherence. In the multivariable regression model adjusted for site, sex, and age, poor adherence was independently associated with tertiary education, absence of heart failure, smoking history, use of VKA prior to index stroke, and prior ischaemic stroke. CHA<sub>2</sub>DS<sub>2</sub>-VASc and SAME-TT<sub>2</sub>R<sub>2</sub> scores were not associated with poor adherence.

**Conclusions:** Adherence was poor in half of AF patients who survived an ischaemic stroke. Independent patient-related factors, rather than composite scores, were associated with poor adherence in these patients.

### KEY MESSAGES

- Adherence was poor in half of the atrial fibrillation patients who survived an ischaemic stroke.
- Independent patient-related factors rather than composite scores were associated with poor adherence.
- The findings support the importance of recognising adherence support as a crucial part of holistic patient care recommended by recent AF guideline.

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## Introduction


Atrial fibrillation (AF) substantially increases the risk of ischaemic stroke, accounting for ~20–38% of all ischaemic strokes [1]. Although oral anticoagulation (OAC) can reduce the risk to approximately one-third, about one-quarter of all ischaemic strokes remain

recurrent [2]. Effective and safe secondary prevention of AF-related stroke relies on strict adherence to and persistence in anticoagulation therapy. However, inadequate or absent anticoagulation treatment is still significantly prevalent and may explain some stroke recurrences in this patient group [1–3].

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Recently, studies in thrombosis prophylaxis showed that non-vitamin-K antagonist oral anticoagulants (NOACs) succeeded compared to warfarin and other vitamin-K antagonists (VKAs) [3]. NOACs overcome some issues encountered with VKAs, namely, the need for regular blood tests, adjusting of doses, and numerous dietary and drug interactions. They have a better safety profile and at least a comparable efficacy profile [3]. Treatment adherence, however, involves many patient-, physician-, and healthcare system-related issues. Although presumed that these strengths of NOACs over VKAs increase adherence and persistence, this remains unestablished [4–6]. Thus, there is an urgent need to research determinants of and obstacles to adherence in and persistence to VKAs and NOACs in specific clinical subgroups.

AF patients with a prior stroke form a specific clinical subgroup with many common factors associated with a higher risk of recurrent stroke risk and potentially increased drug adherence. Older age, renal impairment, higher bleeding and thromboembolic risk scores, previous aspirin use, female sex, and VKA naive status has been associated with the risk of recurrent ischaemic stroke despite anticoagulation [2]. However, similar factors, including older age, higher stroke risk, history of hypertension, diabetes, stroke, and concomitant cardiovascular medication, were found to relate to increased adherence to OACs in the general AF population [4]. Other factors related to increased adherence were once-daily regimen, previous OAC use, and rural living environment [4]. In secondary prevention, poor adherence has been associated with younger age, poor understanding of the medication regimen, cognitive impairment, unstable medication routine, and financial issues [2,7]. Furthermore, neurological status after stroke, fragility, polypharmacy, social isolation, and accessibility to health care and medication may hinder adherence to secondary prevention [7].

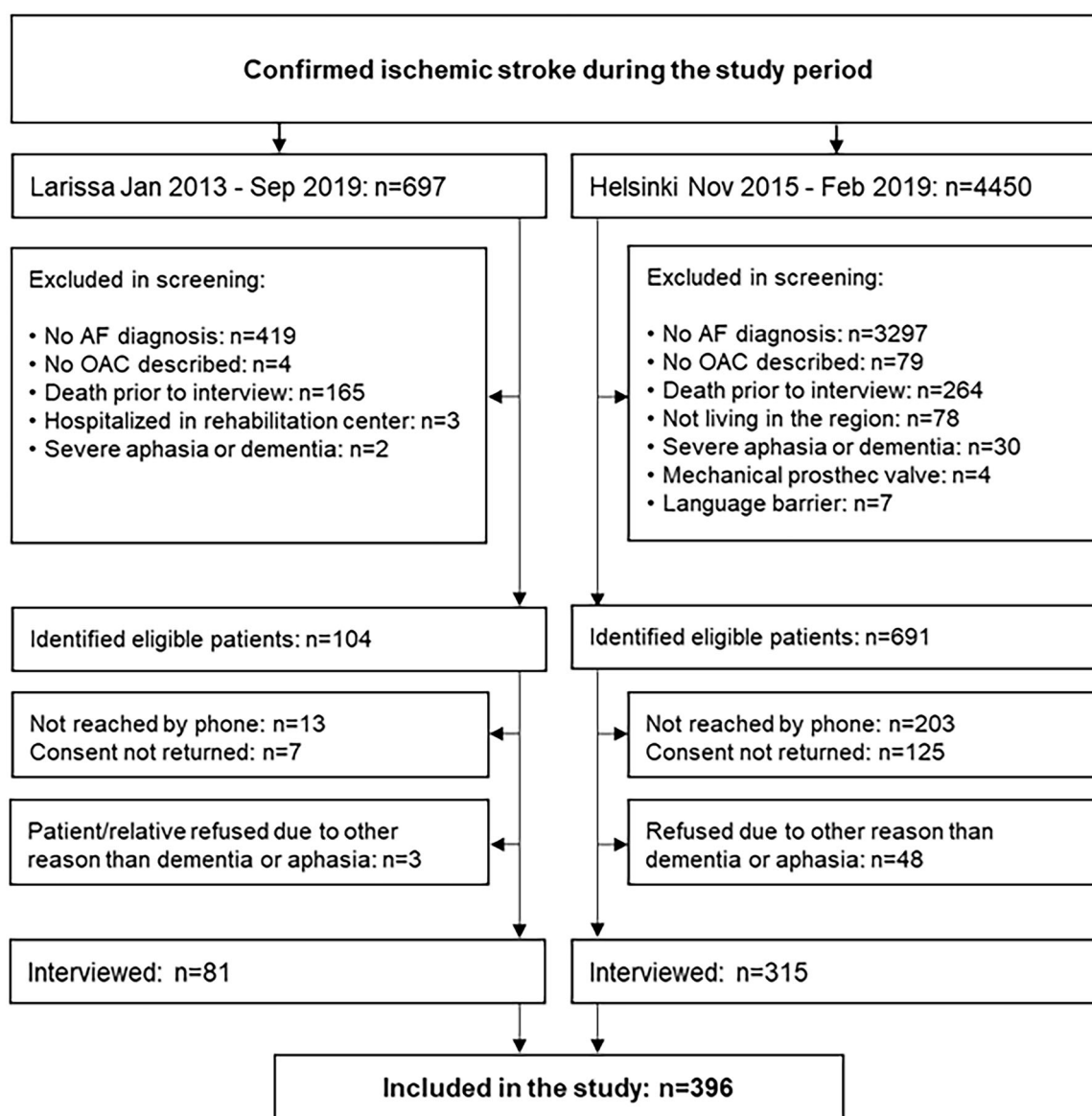
In this cross-sectional study, we used patients interviews with structured questionnaires to investigate patient-reported adherence to oral anticoagulation (OAC) after ischaemic stroke in patients with atrial fibrillation (AF). Together with assessing whether baseline factors were associated with poor adherence, we aimed to assess whether the SAME-TT2R2 (Sex, Age <60 years, Medical history, Tobacco use, non-Caucasian Race) score [3], used to estimate the likelihood of poor INR control in AF patients on VKA therapy, could also be used as an indicator of poor adherence to any-type OAC.

## Methods

To create a sample of patients with atrial fibrillation with suffered ischaemic stroke, we created The Adherence and Persistence to Oral Anticoagulation in AF Patients with Previous Ischaemic Stroke (ADHERE-OAC) dataset. It is based on two prospective stroke registries, the Larissa Stroke Registry (Larissa University Hospital, Greece; started in 01/2013) and the Helsinki Stroke Registry (Helsinki University Hospital, Finland; started in 11/2015), which record all consecutive acute ischaemic stroke patients admitted in the corresponding departments. We searched consecutive strokes from January 2013 to May 2019 in Larissa Registry and from December 2015 to May 2019 in Helsinki Registry and included stroke survivors who had AF, lived in the hospital district area and had an OAC regimen plan at discharge. We excluded patients with mechanical prosthetic valves and those unable to give an interview due to the language barrier, severe aphasia, or dementia (Figure 1). Interviews were conducted between 2018 and 2020, after at least three months from the index stroke.

In Finland, recruited patients were included in the study if written informed consent was obtained. In Greece, all patients or their legally authorised representatives provided either verbal or written informed consent before inclusion in the study. Institutional Review Boards of the participating sites approved the study (Ethics Committee of Helsinki and Uusimaa Hospital District, approval number HUS/1768/2018 and Ethics Committee of University Hospital of Larissa, 13/14/26-07-2018).

Participating patients were interviewed with a structured questionnaire by telephone or in the outpatient clinic. The primary outcome was patient-reported adherence and persistence to OAC regimen. Adherence was defined as the extent to which a patient acts by the prescribed interval and dose of a dosing regimen [8] and assessed by the Adherence to Refills and Medications Scale (ARMS) [9]. The ARMS has been validated against the Morisky Medication Adherence Scale (MMAS-4) questionnaire commonly used to estimate drug adherence, refill adherence using the cumulative medication gap as a parameter, and correlation with blood pressure control [9]. The ARMS includes 14 4-point Likert scale answer options compiling questions about adherence with filling the prescriptions and adherence with taking the medication. The total possible score ranges from 14 to 56, and a higher score indicates poorer adherence. Optimal answers give a score of 17. We considered a score of  $\leq 17$  as good adherence and a score of  $>17$



**Figure 1.** Flowchart of the study sample. AF: atrial fibrillation; OAC: oral anticoagulation.

as poor adherence. Emory University (Atlanta, Georgia, United States) kindly provided a no-cost academic licence to use the ARMS.

We reviewed medical charts for characteristics at the time of discharge from index hospitalisation and recorded demographics (age, sex, ethnicity, time of index stroke, height and weight, education level, and employment status), comorbidities (arterial hypertension, diabetes mellitus, coronary artery disease, prosthetic heart valve, heart failure, peripheral artery disease, dyslipidemia, prior stroke or transient ischaemic attack (TIA), prior major bleeding), lifestyle habits, and antithrombotic treatment before the index stroke.

Index stroke characteristics included NIH Stroke Scale (NIHSS) score, presence of a current ischaemic lesion in the neuroimaging, laterality and arterial

territory of the lesion, presence, and characteristics of chronic ischaemic lesions, leukoaraiosis, haemorrhagic transformation, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) stroke subtype classification, discharge date, and medication (antiplatelet, anticoagulant, antihypertensive, statin, antidiabetic, amiodarone, other medication in use, number of tablets in use per day). In addition, we classified atrial fibrillation as paroxysmal, persistent, permanent, or newly diagnosed [3]. Functional outcome at three months from the index stroke was defined as independent (modified Rankin Scale score, mRS 0–2) or dependent (mRS 3–5).

We used CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Congestive heart failure, Hypertension, Age  $\geq$ 75 years, Diabetes, previous Stroke or transient ischaemic attack, Vascular disease, Age 65–74 years, Sex category female) to

estimate thromboembolic risk at discharge and HAS-BLED score (hypertension, abnormal liver/renal function, history of stroke, bleeding tendency, labile INRs, elderly aged  $\geq 65$  years, drug/alcohol use) to estimate the bleeding risk [3]. SAME-TT2R2 score (Sex, Age  $<60$  years, Medical history, Tobacco use, non-Caucasian Race) was assessed as an indicator of adherence [10].

The interview questionnaire included the ARMS, a telephone version of the Mini-Mental State Examination (Adult Lifestyles and Function Interview-Mini Mental State Examination, ALFI-MMSE) [11], functional status (mRS), and open questions about self-estimated medication adherence. Current medication and the occurrence of recurrent stroke, myocardial infarction, or haemorrhage (major or clinically relevant minor according to the International Society on Thrombosis and Haemostasis definition) [12] were asked from the patients but also checked from the medical records. Social history and demographics at the time of index stroke were further confirmed during the interview.

Continuous data are summarised as medians and interquartile range (IQR) and categorical data as absolute numbers and proportions. For univariate comparisons, we used  $\chi^2$ -test and Fischer's exact test for categorical variables and Mann-Whitney *U*-test for continuous variables. We included variables with significance in univariate analysis or otherwise judged clinically relevant into a binary logistic regression model with a backward stepwise selection method. Poor adherence was treated as a dependent variable. A *P*-value of  $<.05$  was considered statistically significant. Associations of poor adherence to oral anticoagulation are presented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI). All analyses were performed using IBM SPSS Statistics (Armonk, N.Y., USA), version 25.

## Results

From 795 eligible patients identified from the two registries, 579 (73%) were reached. Of these, 396 (69%) consented to participate in the study (Figure 1). The majority (96%) of the participants were interviewed over the telephone. For 9% of the patients, next-of-kin responded to interview questions excluding ALFI-MMSE, which was always answered by the patient or left unfilled if the patient was unable. We excluded from the analysis one patient unwilling to fill in the ARMS questionnaire and three patients without an OAC regimen plan at discharge. The median time

from index stroke hospitalisation discharge to interview was 21 months (IQR 12–33 months).

Table 1 summarises the study participants' characteristics at the time of discharge for index hospitalisation, described by study sites in the online supplement. The median age was 75 years, and 57% were men. Most patients were pensioners (82%) and 41% were prevalent OAC users. The level of education was relatively equally distributed. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score ranged from 2 to 8 while 76% of the patients reached at least 5 risk points. The Median HAS-BLED score was 3; 12% had 2 points and 68% had 3 points. Out of index strokes, 4 out of 5 were cardioembolic, and AF was of new-onset in roughly a third of patients. Table 2 describes the medication at index hospitalisation discharge and at the time of the interview.

At the time of the interview, the median mRS was 1 (IQR 0–2) and most patients lived at home (98%), typically with a spouse or other relative (69%). A total of 307 (78%) patients answered being responsible for their medication, whereas 86 (22%) patients received substantial help with medicines from a relative or other caregiver. ALFI-MMSE responses were obtained from 377 (95%) patients with a median score of 20 (IQR 17–21).

Based on the proportion of patients with ARMS scores over 17, patient-reported poor adherence was 47%, and the median ARMS score was 17 (IQR 17–19). There was no significant difference in ALFI-MMSE scores between those reporting poor adherence compared to those reporting good adherence. Out of warfarin users, 56% and 44% of NOAC users reported poor adherence. Interviewed patients reported more frequently poor adherence than the interviewed relatives (50% vs. 21%). Furthermore, patients responsible for their medication reported more often poor adherence than patients whose medication was taken care of by someone else (50% vs. 37%). The proportion of reported side-effects and the level of OAC knowledge were similar between poor and good adherence groups.

Among patients who reported suboptimal medication implementation (26%), the most commonly self-reported causes were side-effects ( $n=7$ ), personal beliefs about the pros and cons of the medication ( $n=7$ ), and negligence ( $n=7$ ). Specifically, regarding anticoagulation, 22% of patients reported suboptimal implementation of the OAC regimen. That was mostly due to forgetting doses ( $n=35$ ), which was often specified to occur with the evening dose ( $n=15$ ), and when something unusual was happening

**Table 1.** Characteristics of the study sample at discharge from index hospitalisation.

Characteristic	Patients <i>n</i> = 396
Age (years)	
<65	55 (14)
65–74	139 (35)
≥ 75	202 (51)
Median (IQR)	75.0 (70–80)
Sex	
Female	169 (43)
Male	227 (57)
Education	
Primary	128 (32)
Secondary	139 (35)
Tertiary	95 (24)
Unknown	34 (9)
Employment status	
Unemployed	5 (1)
Employed	59 (15)
Pensioner	326 (82)
Other	6 (2)
Unknown	1 (0.3)
BMI (missing in 82)	28 (24–30)
Type of atrial fibrillation	
New-onset	138 (35)
Paroxysmal	142 (36)
Persistent	116 (29)
Comorbidities	
History of ischaemic stroke/TIA	83 (21)
Hypertension	377 (95)
Diabetes	93 (24)
Coronary artery disease	69 (17)
Prosthetic heart valve	7 (2)
Heart failure	34 (9)
Peripheral artery disease	15 (4)
Carotid stenosis	44 (11)
Dyslipidemia	231 (58)
Pulmonary disease	56 (14)
Renal disease	29 (7)
Hepatic disease	5 (1)
Harmful alcohol usage	28 (7)
Active cancer	9 (2)
Prior cancer	33 (8)
Dementia	7 (2)
Prior depression diagnosis	15 (3)
Other mental illness	11 (3)
Intracranial bleeding	9 (2)
Major extracranial bleeding	6 (2)
Smoking	
Current	39 (10)
Stopped during prior 2 years	8 (2)
Stopped > 2 years prior index stroke	148 (37)
Never smoked	201 (51)
Antiplatelet use prior index IS	77 (19)
VKA use prior index IS	101 (26)
NOAC use prior index IS	59 (15)
CHA <sub>2</sub> DS <sub>2</sub> -VASc	5 (5–6)
HAS-BLED	3 (3–3)
HAS-BLED without TTR	3 (3–3)
SAMe-TT <sub>2</sub> R <sub>2</sub>	1 (1–2)
Index stroke characteristics	
NIHSS	4 (2–7)
Chronic lesion	123 (31)
Laterality	
Left	27 (22)
Right	55 (45)
Both	41 (33)
Arterial territory	
ACA	8 (7)
MCA	53 (43)
PCA	35 (29)
Vertebrobasilar	1 (1)
Multiple territories	26 (21)

*(continued)***Table 1.** Continued.

Characteristic	Patients <i>n</i> = 396
Leukoaraiosis	200 (51)
Current lesion	285 (72)
Laterality	
Left	136 (48)
Right	126 (44)
Both	23 (8)
Arterial territory	
ACA	7 (3)
MCA	180 (63)
PCA	63 (22)
Vertebrobasilar	13 (5)
Multiple territories	22 (8)
TOAST	
Large-artery atherosclerotic	11 (3)
Cardioembolism	310 (79)
Small-vessel occlusion	15 (4)
Other determined	1 (0.3)
Undetermined	58 (15)
Functional stroke outcome at 3 months from index stroke	
Dependent	142 (36)
Independent	254 (64)

Data are *n* (%) or median (interquartile range, IQR).

BMI: Body mass index; TIA: transient ischaemic attack; IS: ischaemic stroke; VKA: vitamin-K antagonists; NOAC: non-vitamin K antagonist oral anticoagulants; CHA<sub>2</sub>DS<sub>2</sub>-VASc: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke or transient ischaemic attack, Vascular disease, Age 65–74 years, Sex category female, HAS-BLED: hypertension, abnormal liver/renal function, history of stroke, bleeding tendency, labile INRs, elderly aged ≥ 65 years, drug/alcohol use, TTR: Time in therapeutic range; SAMe-TT<sub>2</sub>R<sub>2</sub>: Sex, Age <60 years, Medical history, Tobacco use, Race; NIHSS: The National Institutes of Health Stroke Scale, or NIH Stroke Scale; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

concomitantly (*n* = 10). Unstable INR was commonly reported in VKA users (*n* = 21), most frequently without specified cause or due to dietary reasons. Ten patients reported some self-regulation of dosing or timing.

In univariate analysis, we found several statistically significant associations between characteristics at discharge and adherence. Patients enrolled in Helsinki reported more commonly poor adherence than in Larissa (55% vs. 16%, *p* < .001). Compared to those with good adherence, patients with poor adherence were younger, more often men, had tertiary education, and were either current smokers or had some smoking history. Prior cancer, prior VKA use, and ischaemic lesion during index hospitalisation were more frequent in patients with poor adherence. They also had milder index strokes, lower CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and less prevalent prior ischaemic stroke or TIA and heart failure ([Online supplement](#)).

In a multivariable regression model adjusted for site, sex and age, poor adherence was independently associated with tertiary education, absence of heart



**Table 2.** Medication at index hospitalisation discharge and at the time of interview.

Medication information	Patients <i>n</i> = 396 (%)
Medication at the hospital discharge	
Antiplatelet medication	25 (6)
Oral anticoagulant	
None	3 (1)
VKA	97 (25)
Apixaban	165 (42)
Dabigatran	69 (17)
Edoxaban	3 (1)
Rivaroxaban	59 (15)
LMWH, therapeutic dose	1 (0.3)
Antihypertensive drug	370 (93)
Statin	359 (91)
Antidiabetic drug	93 (24)
Total number of pills per day	
Median (IQR)	7 (5–9)
Over 5 tablets per day	263 (66)
Oral anticoagulation switch or discontinuation after primarily initiated OAC	
Switched from VKA to NOAC	26 (7)
Switched from VKA to LMWH	3 (1)
Switched from NOAC to VKA	1 (0.3)
Switched from NOAC to NOAC	17 (4)
NOAC dose adjustment	12 (3)
Permanent discontinuation	3 (1)
Medication at the time of interview	
Antiplatelet medication	24 (6)
Oral anticoagulant	
None	9 (2)
VKA	68 (17)
Apixaban	184 (47)
Dabigatran	69 (18)
Edoxaban	4 (1)
Rivaroxaban	61 (15)
LMWH, therapeutic dose	8 (2)
Antihypertensive drug	366 (93)
Statin	339 (86)
Antidiabetic drug	92 (23)
Total number of pills per day	
Median (IQR)	7 (5–10)
Over 5 tablets per day	289 (73)

IQR: interquartile range; OAC: oral anticoagulant; VKA: vitamin-K antagonists; NOAC: non-vitamin K antagonist oral anticoagulants; LMWH: low molecular weight heparin.

failure, smoking history, prior VKA use, and prior index stroke (Table 3). When the CHA<sub>2</sub>DS<sub>2</sub>-VASc was included in the binary regression model and score components excluded, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was not associated with poor adherence (OR 0.89, 95% CI 0.74–1.07). Similarly, when the SAME-TT<sub>2</sub>R<sub>2</sub> was included in the binary regression model and score components excluded, the SAME-TT<sub>2</sub>R<sub>2</sub> was not associated with poor adherence (OR 0.94, 95% CI 0.74–1.19).

## Discussion

Adherence and persistence stand mandatory for the effectiveness of any medication regimen. Patient perception of medication is an integral part of adherence but is often overlooked by studies, presumably because of its subjective nature. Our research found that patient-reported poor adherence to medication among patients with AF after an ischaemic stroke was common and associated with a higher level of education, absence of heart failure, smoking history, and use of VKA before index stroke. There was no significant difference between different OACs. The SAME-TT<sub>2</sub>R was not associated with poor adherence. Only 1% of the participants reported permanent discontinuation of the OAC treatment.

In our study, 47% of patients reported poor adherence based on ARMS scores over 17. Our observation indicates worse adherence in stroke survivors compared to a recent meta-analysis in AF patients in general, which reported that the pooled mean adherence was 77% at six months and 74% at one year [4]. Another review showed 66% of good adherence [5]. These studies included mainly studies using medical

**Table 3.** Association of poor adherence (AMRS score >17) to oral anticoagulation and patient characteristics in patients with prior ischaemic stroke (binary logistic regression model).

Covariates	All variables; OR (95% CI)	Best fitting model; OR (95% CI)	<i>p</i> -value
Site (Larissa as reference)	5.20 (2.36–11.49)	5.20 (2.36–11.49)	<.001
Age	1.00 (0.97–1.02)	...	.799
Male sex	1.18 (0.73–1.91)	...	.528
Education			.007
Primary	0.53 (0.29–0.97)	0.50 (0.28–0.90)	.022
Secondary	0.45 (0.25–0.81)	0.41 (0.23–0.73)	.002
Tertiary	Reference	Reference	
New-onset AF	0.75 (0.45–1.25)	...	.327
Heart failure	0.37 (0.16–0.86)	0.40 (0.18–0.91)	.029
Prior cancer	1.54 (0.70–3.40)	...	.300
Previous stroke or TIA	0.61 (0.34–1.10)	...	.094
Smoking history	1.44 (0.90–2.95)	1.59 (1.03–2.46)	.037
High-risk alcohol consumption	1.24 (0.52–2.29)	...	.675
VKA use prior index stroke	1.47 (0.79–2.74)	1.81 (1.10–3.00)	.020
NIHSS	0.97 (0.93–1.02)	...	.246
Current lesion	0.80 (0.44–1.45)	...	.470
VKA vs. NOAC (reference) at discharge	1.29 (0.73–2.26)	...	.337
Polypharmacy*	1.06 (0.65–1.74)	...	.854

OR: odds ratio; 95% CI: confidence interval; AF: atrial fibrillation; TIA: transient ischaemic attack; VKA: vitamin-K antagonists; NIHSS: NIH Stroke Scale. \*Total number of pills at discharge over 5.

adherence estimates based on prescription refills, namely proportional days covered (PDC) and medication possession ratio (MPR), and excluded studies with patient-reported adherence. Both studies concluded limited results regarding adherence to VKA and no direct comparison between NOACs and VKA were done.

We did not find significant differences in patient-reported poor adherence between VKA and NOAC users in ischaemic stroke survivors. These findings are similar to a systematic review on patient-reported outcomes associated with OACs, including four studies reporting adherence in the AF population, all using MMAS-8 questionnaire to adherence estimation [6].

In univariate comparison, we identified several variables that were associated with poor adherence. However, only higher education, absence of heart failure, smoking history and VKA use prior index stroke remained significant in binary regression analysis adjusted for age, sex, and study site. A study on NOAC-treated AF patients found that naïve status and higher comorbidity were associated with poor adherence. Older age and a higher number of concomitant medications predicted better adherence [13]. A systematic review on adherence in secondary prevention after stroke or transient ischaemic attack found a high heterogeneity between studies. Frequently reported factors hindering adherence were concerns about treatment, increased disability, severe stroke, polypharmacy, and complex medication regimen but all factors were non-significant in the meta-analysis [14].

We did not find an association between the SAME-TT<sub>2</sub>R<sub>2</sub> score and adherence. However, the TREATS-AF trial, currently conducted in Thailand, investigates whether a SAME-TT<sub>2</sub>R<sub>2</sub>-guided strategy for the selection of the anticoagulant in AF patients has an impact on clinical outcomes of efficacy and safety [15].

Our study has strengths and limitations. Our study represents a real-world setting and assessed patient perception of medication rather than registry-based use of drugs. For that type of research, the sample size is relatively large. However, some selection bias is possible as we could not contact all the potentially eligible patients. Unfortunately, as consent was a prerequisite for inclusion, neither could we compare demographics and morbidities between participants and those not included. Our patient sample represents mainly independent patients with low-level disabilities and living at home and mostly taking care of their medication by themselves. Nevertheless, by systematically including patients in nursing homes or more reliable on others on medication, the adherence most likely would be better. Finally, recall bias is possible.

As medical professionals conducted the study, participants might have assessed their adherence more positively than it was.

There are most likely some cultural differences that explain the surprisingly large difference in reported adherence between sites and could reflect some recall bias. However, as reported in the online supplement, we also found that interviewed patients in Larissa were older and less educated. Patients in Finland were more often living alone, took more often care of their medication. Furthermore, most of the interviews (98%) in Finland were given by patients, while some next-in kin were interviewed in 44% of cases in Greece. These factors, many related to family settings, could also explain the differences in reported adherence between the study sites.

Our study did not collect information about mechanisms patients used to support their medication adherence, although some patients spontaneously described some, like using a good pillbox. However, our patients reported issues with remembering to take the drugs and concerns about potential side effects. Our study highlights the need to integrate adherence support into patient care. In the future, research about adherence supporting mechanisms found efficient by the patients themselves would be valuable. Regular follow-up visits, direct asking about medication adherence, and ensuring enough time to discuss and use motivational interviewing methods could be efficient. As a part of the holistic care of AF patients, clinicians should offer patient-centered individualised tools to support adherence.

## Conclusions

Our study supports the importance of recognising adherence support as a crucial part of holistic patient care recommended by recent AF guidelines.

## Author contributions

JP, GN, and ML contributed substantially to the conception, study design, execution, data analysis, interpretation, and revision of the manuscript. PT contributed substantially to study implementation, acquisition, analysis, and interpretation of the data and drafting and revising the manuscript. IL, JK, IS, EK, and DS contributed substantially to the acquisition and interpretation of data and revision of the manuscript. All authors approved the publication of the revised manuscript.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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