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ORIGINAL ARTICLE
Atrial fibrillation

Long-term persistence and adherence with non-vitamin K oral anticoagulants in patients with atrial fibrillation and their associations with stroke risk

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Aims Studies on adherence and persistence with non-vitamin K oral anticoagulant (NOAC) treatment have relied on data from the early years of NOAC availability. We aimed to study long-term adherence and persistence with NOACs and their association with stroke risk.

Methods and results From the Stockholm Healthcare database, we included 21 028 atrial fibrillation patients claiming a first NOAC prescription from July 2011 until October 2018, with more than 1000 patients having more than 5 years of follow-up (median: 2.0, interquartile range: 1.0–3.2). Persistence rates, defined as continuing to claim NOAC prescriptions within a 90-day gap, decreased to 70% at the end of follow-up. However, 85% of the patients were treated at the end of the study due to reinitiations. Adherence, calculated as medication possession rate (MPR) in 3 and 6-month intervals among persistent users, remained stable at 90%, with 75% of patients having an MPR >95% throughout the study period. Using a case–control design, we calculated associations of persistence and adherence with stroke risk, adjusting for potential confounders. The outcome was a composite of ischaemic or unspecified stroke and transient ischaemic attack. Non-persistence and poor adherence were both associated with increased stroke risk [non-persistence adjusted odds ratio (aOR): 2.05; 95% confidence interval (CI): 1.49–2.82, 1% reduction MPR aOR: 1.03; CI: 1.01–1.05]. There was no association between non-persistence or poor adherence and the falsification endpoints; fractions and respiratory infections, indicating no 'healthy-adherer' effect.

Conclusion Persistence rates decreased slowly over time, but persistent patients had high adherence rates. Both non-persistence and poor adherence were associated with an increased stroke risk.

Keywords Atrial fibrillation • NOAC • Oral anticoagulants • Adherence • Persistence • Stroke

Introduction

Non-vitamin K oral anticoagulants (NOACs) are the preferred oral anticoagulants (OACs) for stroke prevention in patients with atrial fibrillation (AF) according to current guidelines.[1,2] Besides their efficacy and safety compared to vitamin K antagonists (VKAs) as shown in both randomized clinical trials[3] and in observational studies,[4–6] the NOACs do not require regular monitoring of prothrombin time

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through international normalized ratio (INR). However, measuring the INR is a useful tool to monitor the intensity of treatment and may improve the adherence and persistence with VKA therapy. As a consequence of the lack of monitoring, guidelines stress the importance of actively promoting adherence and persistence to NOAC treatment.[1,2] Contrary to the VKAs, the NOACs have short half-lives and the protection against ischaemic stroke wanes rather rapidly, making adherence and persistence to NOAC treatment even more important.[7]

Several studies have assessed the adherence and persistence to NOAC treatment in patients with AF.[8–10] However, these studies were conducted in the period shortly after marketing approval of NOACs. The most recent article included in a systematic review from 2019, was a study from China with data until 2017 and a maximum of 36 months of follow-up, but the vast majority of studies included in this systematic review only had data until 2014 and shorter follow-up.[10] Studies on adherence and persistence with longer follow-up are missing, as well as recent studies on medication behaviour when NOACs have become the mainstay in stroke prevention in AF patients. Studies that have assessed associations of poor adherence and non-persistence with clinical outcomes have also relied on data from the early years of NOAC availability.[11,12] In these early years, the initiation and follow-up of NOAC treatment were most likely concentrated to doctors with special interest in AF, whereas this treatment has now shifted towards primary care. In addition, previous work has shown that the pattern of antithrombic treatment in AF has changed since the introduction of the NOACs when aspirin treatment was common and OACs markedly underused.[13] The aim of this study was to describe the long-term adherence and persistence to NOAC treatment in AF patients and to assess associations between poor adherence and persistence to NOAC treatment and stroke risk.

Methods

Database

We used the Stockholm healthcare database for this population-based study.[14] It contains demographic and diagnostic data, and pharmacy claims of all prescription drugs for all 2.3 million inhabitants in the Stockholm region. Diagnostic data (ICD-10 codes) cover both inpatient care, specialist ambulatory care, and primary care. The pharmacy claims data are from the Swedish prescribed drug registry, containing data on all pharmaceutical claims for prescription drugs in Sweden.[15]

Patient selection

From the Stockholm healthcare database, we created a cohort of all patients initiated on NOAC treatment with a known history of AF (ICD-10: I48) who, after a wash-out period of 1 year, claimed a first prescription for a NOAC from July 2011 until October 2018. We excluded patients with a warfarin prescription or a diagnosis code for deep venous thromboembolism or a procedure code for knee/hip replacement surgery in the year before the cohort inclusion date, the latter to remove those with indications for short-term NOAC treatment (see Supplementary material online, *Appendix Table S1* for ICD-10 and procedure codes). Patients in the cohort were followed until they claimed a warfarin prescription, died, moved out of the region, or the end of the study period being October 2018.

Long-term persistence and adherence

We partitioned the follow-up time into 3-month periods during the first year of follow-up and 6-month periods in the years thereafter. For each interval, we assessed persistence and adherence in the cohort. We used shorter periods in the first year, as we expected that changes in persistence and adherence would occur more frequently during the first year of treatment.

We considered patients to be persistent if they claimed a new NOAC prescription within 91 days after the calculated end of supply from a prior prescription. If patients had the same NOAC available from a previous prescription before claiming a new prescription, the additional days theoretically covered were added to their new prescription.[16] The maximum number of spillover days was set at 91 days. Patients could switch between NOACs and still be considered persistent. If the patient failed to claim a new prescription within the given gap, we defined the date of non-persistence at the calculated end of supply from the last prescription. For the first day of each interval, we calculated the proportion of persistent users by dividing the number of persistent users by the number of patients in the cohort. In addition, we assessed the proportion of patients who had a bleeding event in the 180 days prior to non-persistence, as this might be a reason for discontinuation (see Supplementary material online, *Appendix Table S1* for ICD codes).

As patients may restart their treatment after being considered non-persistent, we performed an additional analysis in which we defined the proportion of patients having a NOAC available at the start of each interval.[17] With that, it is possible to capture patients restarting treatment after non-persistence and to calculate the actual proportion of patients receiving treatment at a certain point in time.

We only measured adherence in persistent users, to avoid mixing non-adherence and non-persistence. Adherence was measured using the medication possession rate (MPR).[16] For each interval, we divided the number of days a NOAC was available by the number of days in the interval. Similarly, as for persistence, we took stockpiling from previous prescriptions into account. We further categorized the MPRs as >95%, 95–91%, 90–81%, 80–71%, 70–61%, and <61%.

In addition, to analyse whether persistence and adherence changed over time, we measured persistence and perfect adherence (>95% MPR) during the first year of treatment. For this, we selected patients who were not censored during their first year of treatment.

Association of non-persistence and non-adherence with stroke risk

Case–control selection

To assess the associations of non-persistence and poor adherence with stroke risk, we performed a nested case–control study, the details of which are explained in the Supplementary material online, *Appendix eMethods* section (see Supplementary material online, *Appendix Figure S1a* and *b* for a visual presentation of the study design).[18] In short, cases were patients suffering from a composite endpoint of ischaemic stroke, unspecified stroke, and transient ischaemic attack (TIA), registered in ICD-10 codes as a primary or secondary diagnosis in secondary inpatient care, and requiring acute care (See Supplementary material online, *Appendix Table S1* for ICD-10 codes). We used incidence density sampling to match up to five controls on sex and age. We defined non-persistence and poor adherence as stated above. Adherence was defined as the MPR in the year prior to the event.

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Table 1 Baseline cohort characteristics

Characteristics	Number of patients (%)
Age at index date, mean (SD)	73.61 (10.96)
0–6	3745 (17.8%)
65–74	7299 (34.7%)
75–84	6474 (30.8%)
85+	3510 (16.7%)
Female	9315 (44.3%)
Type of NOAC	
Dabigatran	3172 (15.1%)
Rivaroxaban	2009 (9.6%)
Apixaban	15 810 (75.2%)
Edoxaban	37 (0.2%)
Year of inclusion	
2011	84 (0.4%)
2012	588 (2.8%)
2013	1586 (7.5%)
2014	2289 (10.9%)
2015	3853 (18.3%)
2016	4456 (21.2%)
2017	5100 (24.3%)
2018 (up to October)	3072 (14.6%)
CHA_2DS_2-VASc, mean (SD)	3.29 (1.92)
0	1054 (5.0%)
1	2619 (12.5%)
2	4126 (19.6%)
3	4563 (21.7%)
4	3772 (17.9%)
5	2036 (9.7%)
6	1234 (5.9%)
7	1079 (5.1%)
8	473 (2.2%)
9	72 (0.3%)
Hypertension	13 699 (65.1%)
Anaemia	2343 (11.1%)
Abnormal liver function	363 (1.7%)
Renal disease	1329 (6.3%)
Alcoholism	776 (3.7%)
Prior bleed	2034 (9.7%)
Previous stroke/TIA/embolism	4191 (19.9%)
Myocardial infarction	1155 (5.5%)
Heart failure	3420 (16.3%)
Vascular disease	4370 (20.8%)
COPD	3305 (15.7%)
Rheumatoid arthritis	983 (4.7%)
Diabetes	3535 (16.8%)
Cancer	2508 (11.9%)
Aspirin	8137 (38.7%)
Clopidogrel	862 (4.1%)
Other antiplatelets	417 (2.0%)
NSAID	2244 (10.7%)
Corticosteroid	1666 (7.9%)
Diuretic	4341 (20.6%)
Beta-blocker	11029 (52.4%)
Ca channel blocker	5503 (26.2%)
RAAS inhibitor	8036 (38.2%)
Statin	5965 (28.4%)
Oral antidiabetic drug	1858 (8.8%)
Insulin	956 (4.5%)
Antidepressant	2353 (11.2%)

Baseline characteristics of all patients included in the cohort.
COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin–angiotensin–aldosterone antagonist; TIA, transient ischaemic attack.

Covariates

For comedication, we included drugs that might be associated with stroke risk. We searched for the following claims during 6 months prior to the cohort inclusion date: aspirin, clopidogrel, other antiplatelets, non-steroidal anti-inflammatory drugs, corticosteroids, diuretics, beta-blockers, calcium channel blockers, renin–angiotensin–aldosterone antagonist inhibitors, statins, oral antidiabetics, insulin, and antidepressants. For comorbidities, we searched for components of the CHA_2DS_2-VASc score, the HAS-BLED score, and other complicating comorbidities during 5 years prior to the cohort inclusion date: heart failure, hypertension, prior stroke/TIA/embolism, vascular disease, diabetes renal disease, liver disease, prior bleed, anaemia, alcoholism; chronic obstructive pulmonary disease, cancer, and rheumatoid arthritis (see Supplementary material online, *Appendix Table S1* for ICD-10 and ATC codes).

Statistical analysis

We used descriptive statistics to present persistence and adherence rates in different intervals. To assess if adherence and persistence changed over time, we used logistic regression to calculate the odds ratios (ORs) for persistence and perfect adherence (MPR >95%) during the first year of treatment. Both models included a continuous variable for the year of cohort inclusion, to test if there was a significant trend over time for the proportion of patients being persistent and adherent in the first year of treatment. All models were adjusted for age, sex, and the aforementioned covariates.

The statistical analysis of the case–control study is described in the Supplementary material online, *Appendix eMethods* section. In short, we used conditional logistic regression to test the associations of non-persistence or poor adherence with stroke risk, adjusting for the aforementioned covariates.

Sensitivity analyses

We performed several sensitivity analyses, presented in Supplementary material online, *Appendix eMethods* section. In short, in one analysis, we excluded patients with a CHA_2DS_2-VASc score of 0 or 1, who may have an indication for short-term NOAC treatment when they undergo cardioversion. Secondly, we performed analyses using falsification endpoints, to disentangle the potential 'healthy adherer' effect.[19] Thirdly, we performed an analysis with a definition of non-persistence after a gap of 182 days and an analysis with measuring adherence in the 182 days prior to the event. Finally, we assessed persistence for each different NOAC.

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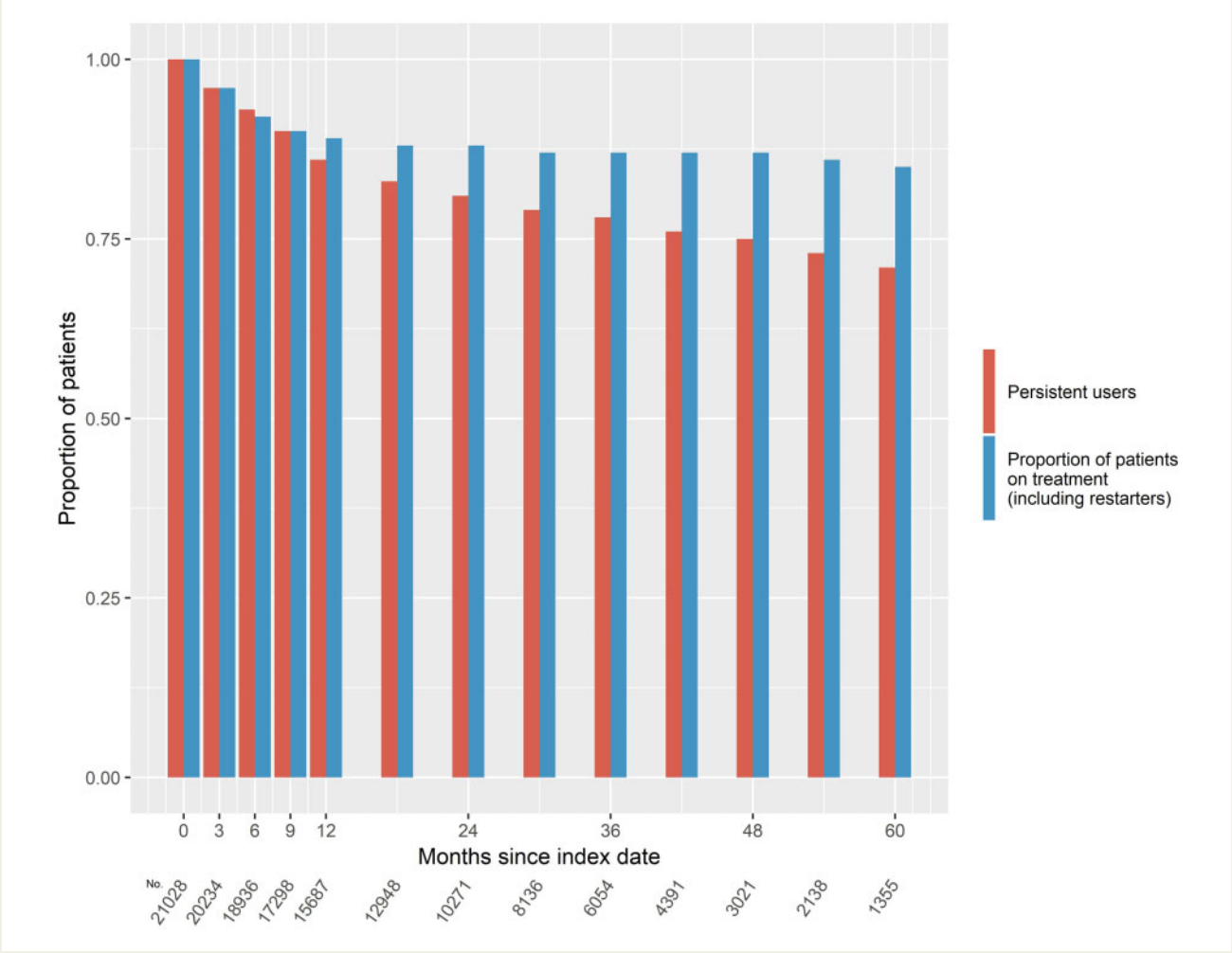

Figure 1 Number of persistent users and proportion of patients on treatment at each interval during follow-up. The numbers below represent the number of patients that are in the cohort at the beginning of each interval.

Results

In total, we included 21 028 AF patients who were newly initiated with a NOAC, of whom 15 810 (75.2%) started with apixaban. Their mean age was 73.6 (SD 11.0) years and 44.3% were female. The median follow-up time was 2.0 years (interquartile range: 1.0–3.2) with a maximum of 7.4 years and more than 1000 patients had more than 5 years of follow-up (see Supplementary material online, *Appendix Figure S2*). During follow-up, 905 patients switched to VKA treatment and were censored. Hypertension was the most common comorbidity (65.1%) and beta-blockers were the most commonly used drugs at baseline (52.4%) (*Table 1*). The stroke risk in the population was comparable to that found in other large registries.[20]

Persistence and adherence

Persistence rates declined the most in the first year of treatment, to ~85%, and subsequently decreased steadily to ~70% at the end of the study. When including patients restarting treatment, we found that the proportion of patients receiving treatment declined to ~85% after 1 year and remained stable at that rate, while the proportion of fully persistent users kept declining (*Figure 1*). There were no large differences in persistence with different NOACs, but the persistence with apixaban and rivaroxaban was better than that for dabigatran. However, numbers for rivaroxaban and dabigatran treated patients were low (Supplementary material online, *Appendix Figure S4*). Among the 3270 patients who became non-persistent, 212 patients experienced a bleeding event in the 180 days prior to this date (6.5%).

Among the patients who were persistent, the MPR remained stable at around 90%. Approximately 75% of them had an MPR >95% throughout the study (*Figure 2*).

*Figure 3*shows that the proportion of patients with perfect adherence (MPR >95%) and with persistent use in the first year increased with each year. Results from the logistic regression show that there was a significant trend towards increasing persistence and adherence over the years, after adjusting for baseline characteristics. The adjusted odds ratio (aOR) for being persistent increased by 1.11 [95% confidence interval (CI): 1.07—1.14] for each additional year,

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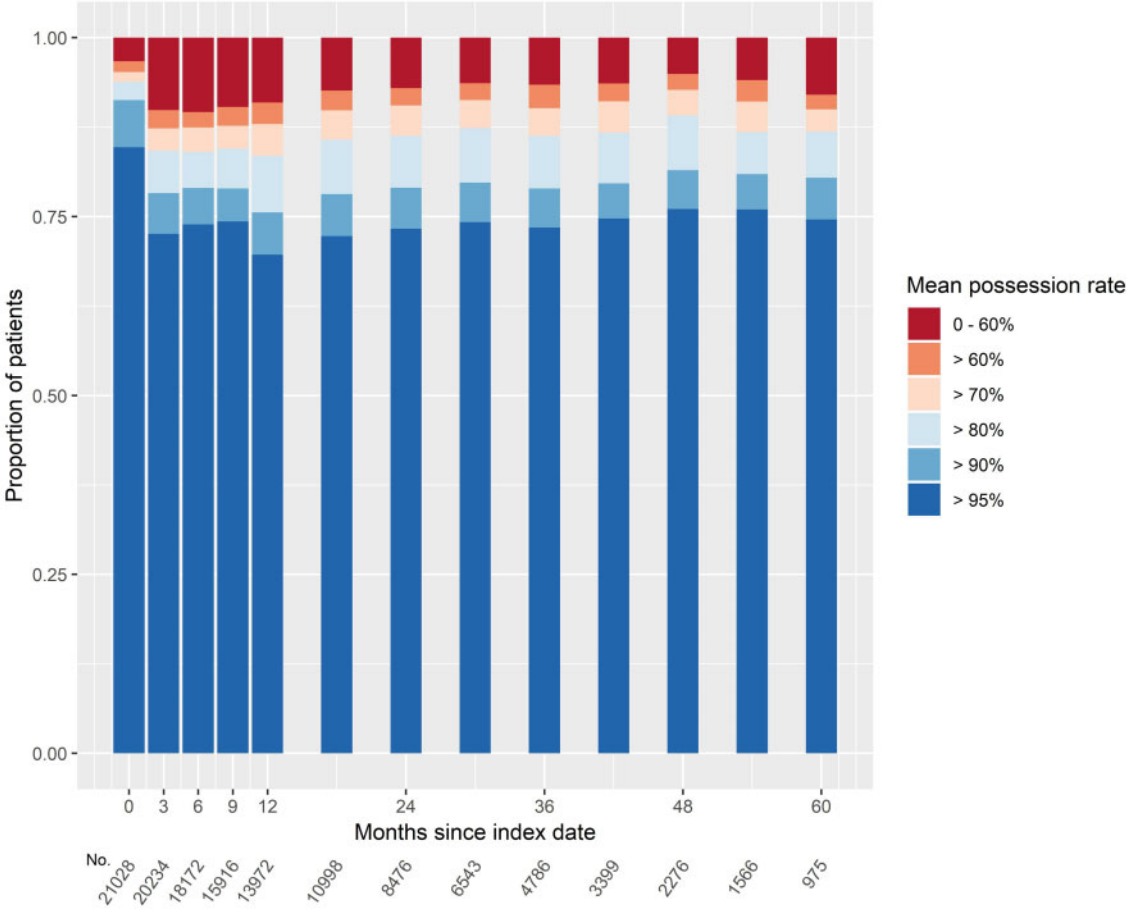

Figure 2 Proportion of patients in each category of the mean possession rate for each interval during follow-up. MPR, mean possession rate.

and for being perfectly adherent, this aOR was 1.04 (95% CI: 1.02—1.07).

Associations with stroke risk

During follow-up, 454 patients suffered a stroke or a TIA and 452 of them were included as cases for the analysis of non-persistence. Two cases could not be matched to a control. The 452 cases were matched to 2252 controls. In four cases, fewer than five controls could be matched. Of the 454 patients suffering a stroke or TIA, 139 were persistent users and were on treatment for at least a year and were thus eligible as cases for the analysis of poor adherence. The 139 patients included as cases were matched to 690 controls in the adherence analysis. In two cases, fewer than five controls could be matched. Baseline characteristics of the case–control sets, along with the MPRs and non-persistence rates, are presented in *Table 2*.

Non-persistence was associated with an increased stroke risk (aOR: 2.05; CI: 1.49–2.82). The increased risk for stroke/TIA appeared not to occur directly after becoming non-persistent (*Figure 4*), and there was no association between time since non-persistence and stroke risk (aOR: 0.89; CI: 0.63–1.60).

Decreased adherence was associated with an increased stroke risk (*Figure 4*). When analysing adherence as a continuous variable we found that a 1% decrease in the MPR was associated with a 3% increase of stroke risk (aOR: 1.03; CI: 1.01–1.05). The logistic regression with categorical MPRs showed that for each reduction in MPR category, the odds ratio for a stroke was 1.43 times higher (aOR: 1.43; CI: 1.11–1.86).

Sensitivity analyses

The results of the sensitivity analyses are in the Supplementary material online, *Appendix eResults* section. In short, the results of the sensitivity analyses were in line with the main analysis, the falsification endpoints showed a neutral association, and there were no large differences in persistence with the different NOACs.

Discussion

In the current population-based cohort study with more than 1000 patients having over 5 years of follow-up, we found that persistence rates declined steadily throughout follow-up, from 85% after the first year to 70% at the end of the study, while adherence rates remained stable. However, many non-persistent patients reinitiated therapy and the proportion of patients actually receiving NOAC treatment

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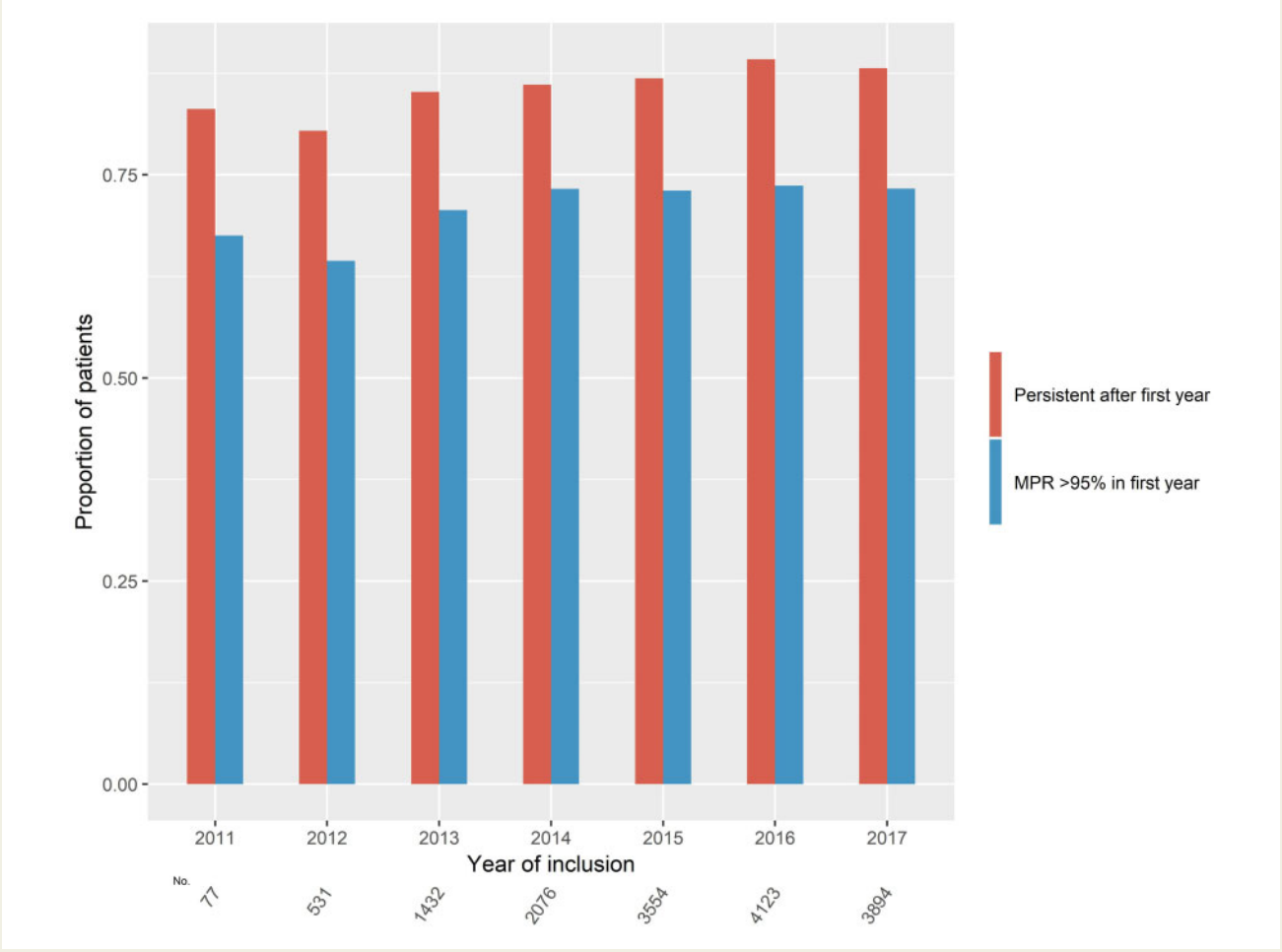

Figure 3 Proportion of patients that are persistent after 1 year and proportion of patients that have perfect adherence (mean possession rate >95%) in their first year of treatment, stratified per inclusion year.

remained stable around 85% during the entire follow-up. Persistence and adherence during the first year of treatment increased significantly over time. Importantly, both non-persistence and poor adherence were associated with an increased stroke risk.

Both persistence and adherence are required for a drug to have a clinical effect, especially for NOACs, given their short half-lives.[7] There was no correlation between the time since non-persistence and an increasing stroke risk. This finding is as expected if there is no rebound procoagulant effect upon discontinuation. Patients rapidly lose their protection against stroke when they stop taking the NOAC, but this risk should not change after a longer period of being unprotected. However, the increased risk was not visible in the first 31 days of non-persistence. Some patients may still have had the drug available due to poor adherence, and this might partly explain the lack of an increased stroke risk immediately after being defined as non-persistent.

For adherence, there was a linear correlation between the degree of non-adherence and the risk for stroke, stressing the importance of improving adherence in patients.[21] *Figure 3* shows that the risk of suffering a stroke is clearly increased when the MPR is below 80%. An additional analysis showed no further increase in stroke risk when the MPR was further reduced below 80%. We found that the protective effect of the NOACs was intact at an MPR above 90%. This is in line with a recent Korean study with data up to 2016, also showing a protective effect above 90%.[22] These two studies in different settings emphasize that clinicians and patients should strive for an MPR >90%. Future studies on anticoagulant adherence should abandon the frequently used MPR >80% as a binary cut-off for adherence or non-adherence,[10] as the protective effect of NOAC treatment is maintained at an MPR >90%.

The proportion of persistent patients declined steadily after an initially larger drop, while adherence rates remained stable. Importantly, when incorporating reinitiators, we found that ~85% of the patients were on NOAC treatment throughout the study period. Previous studies have reported persistence rates after 2 years ranging from 80% to below 30%, thus persistence rates were high in the current study.[10] Interestingly, both persistence and adherence rates in the first year of follow-up of each patient increased year by year from

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Table 2 Baseline characteristics of cases and controls

	Persistence		Adherence	
	Cases	Controls	Cases	Controls
Number of patients	452	2252	139	690
Non-persistence	78 (17.3%)	222 (9.9%)	NA	NA
MPR (SD)	NA	NA	90.46 (12.30)	93.57 (9.67)
Age at index date, mean (SD)	76.73 (9.93)	76.66 (9.97)	76.76 (8.46)	76.49 (8.68)
Female	209 (46.2%)	1042 (46.3%)	60 (43.2%)	297 (43.0%)
Hypertension	327 (72.3%)	1494 (66.3%)	100 (71.9%)	447 (64.8%)
Anaemia	55 (12.2%)	268 (11.9%)	20 (14.4%)	68 (9.9%)
Abnormal liver function	7 (1.5%)	30 (1.3%)	3 (2.2%)	15 (2.2%)
Renal disease	29 (6.4%)	123 (5.5%)	11 (7.9%)	41 (5.9%)
Alcoholism	25 (5.5%)	66 (2.9%)	8 (5.8%)	13 (1.9%)
Prior bleed	55 (12.2%)	210 (9.3%)	17 (12.2%)	71 (10.3%)
Stroke/TIA/embolism	114 (25.2%)	498 (22.1%)	29 (20.9%)	141 (20.4%)
Myocardial infarction	39 (8.6%)	128 (5.7%)	11 (7.9%)	42 (6.1%)
Heart failure	54 (11.9%)	356 (15.8%)	14 (10.1%)	130 (18.8%)
Vascular disease	75 (16.6%)	476 (21.1%)	21 (15.1%)	157 (22.8%)
COPD	65 (14.4%)	337 (15.0%)	24 (17.3%)	108 (15.7%)
Rheumatoid arthritis	19 (4.2%)	117 (5.2%)	4 (2.9%)	33 (4.8%)
Diabetes	75 (16.6%)	335 (14.9%)	24 (17.3%)	94 (13.6%)
Cancer	68 (15.0%)	284 (12.6%)	24 (17.3%)	82 (11.9%)
Aspirin	235 (52.0%)	1046 (46.4%)	90 (64.7%)	346 (50.1%)
Clopidogrel	17 (3.8%)	100 (4.4%)	5 (3.6%)	33 (4.8%)
Other antiplatelets	6 (1.3%)	44 (2.0%)	3 (2.2%)	19 (2.8%)
NSAID	41 (9.1%)	199 (8.8%)	12 (8.6%)	74 (10.7%)
Corticosteroid	28 (6.2%)	165 (7.3%)	6 (4.3%)	58 (8.4%)
Diuretic	113 (25.0%)	511 (22.7%)	41 (29.5%)	162 (23.5%)
Beta-blocker	250 (55.3%)	1254 (55.7%)	85 (61.2%)	398 (57.7%)
Ca channel blocker	114 (25.2%)	582 (25.8%)	40 (28.8%)	181 (26.2%)
RAAS inhibitor	195 (43.1%)	867 (38.5%)	66 (47.5%)	259 (37.5%)
Statin	108 (23.9%)	656 (29.1%)	43 (30.9%)	221 (32.0%)
Oral antidiabetic drug	33 (7.3%)	163 (7.2%)	10 (7.2%)	52 (7.5%)
Insulin	20 (4.4%)	84 (3.7%)	9 (6.5%)	27 (3.9%)
Antidepressant	51 (11.3%)	244 (10.8%)	17 (12.2%)	78 (11.3%)

Baseline characteristics and measures of persistence and adherence of cases and controls, for both the persistence and the adherence associations.
COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin–angiotensin–aldosterone antagonist; TIA, transient ischaemic attack.

2011 to 2018. This indicates that a shift of NOAC treatment away from specialist care did not lead to worsened persistence or adherence.

Our results are in line with previous studies showing an increased stroke risk with lower adherence rates.[11,12,22,23] However, these studies did not take non-persistence into account, and their results appear to be a combined effect of patients having stopped the treatment and patients being non-adherent while treated. Our approach to only measure adherence in patients who were considered to be persistent users reflects the effect of poor adherence on stroke risk more precisely. Compared to previously published adherence rates from a systematic review,[8] the adherence rates in our study are amongst the highest. Again, this can be explained by only measuring adherence in patients who were still persistent users. In addition, we found that adherence and persistence rates increased over time. Therefore, having more recent data can also partially explain higher adherence in our study.

We did not have access to explanations for non-persistence since patients in our cohort could not be identified and contacted to collect additional information, but bleeding might be a reason for discontinuation of NOAC therapy, as well as dyspepsia during dabigatran treatment. A study from Denmark examined events preceding NOAC discontinuation and reported that 7.6% of the patients experienced a bleed prior to discontinuation, which is in line with the 6.5% we found.[24]

Our study has several strengths. First, we distinguish between adherence and persistence and only measured adherence in patients who were actually still on treatment. With that approach, we describe clinical practice more precisely, since there is a clear difference between stopping the treatment and not taking the treatment as

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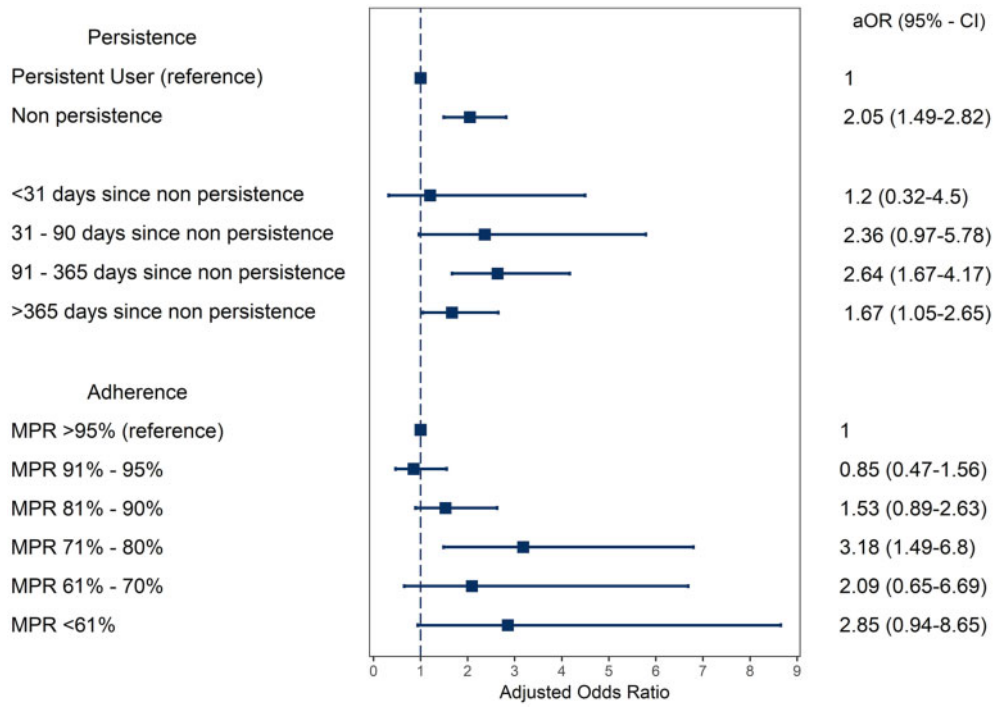

Figure 4 Adjusted odds ratios for the association of non-persistence or poor adherence and the risk for stroke. aOR, adjusted odds ratio; MPR, mean possession rate.

intended. In addition, we did not split adherent and non-adherent patients at a clinically meaningless MPR of 80% but treated adherence as a continuous variable. Our results show that an MPR of ≥90% would be a more reasonable cut-off if adherence is treated as a binary variable. Second, we are the first to present adherence and persistence with a long follow-up time and including more contemporary data which reflect the current panorama of treatment and treating doctors. As NOACs usually are to be used life-long by AF patients, persistence and adherence beyond the first couple years of treatment are important. Third, the VAL database is a complete population database, including diagnoses from both specialist care and primary care, and data on all claimed prescriptions. This results in a full picture of all patient's healthcare consumption in a complete healthcare setting. Previous work from the region has shown that 12% of AF patients would not be captured if only secondary care data were used, indicating the importance of having data from all levels of care.[13,14] In addition, the VAL database contains pharmacy claims data which provide dependable indices of persistence.[21] Relying on prescription data involves uncertainty as to whether the patient had claimed the prescription and would also require that all potential prescribers were accessed in the database.[25] Fourth, we used falsification endpoints and other sensitivity analyses, indicating that our results are not likely explained by a 'healthy-adherer' effect and that our results are not sensitive to the definitions chosen for non-persistence. Finally, we used advanced methods to measure adherence, taking stockpiling from previous prescriptions into account.

Our study also has some limitations. First, with pharmacy claims data, we cannot assure whether and exactly how patients actually took the treatment. In addition, it is impossible from pharmacy claims data to distinguish between patients who take drug holidays and patients who regularly forget to take their medication, which can ultimately affect the risk for ischaemic events. However, it is very likely that non-persistent patients were not taking any drug as they no longer claimed prescriptions and, similarly, it is very likely that patients with poor adherence were skipping doses. Second, when relying on observational data, one can never rule out residual confounding. However, observational data are needed to evaluate treatments in ordinary healthcare, and we found no associations between adherence or persistence and falsification endpoints, i.e. no signs of residual confounding. Third, for the association of non-adherence with stroke risk, we only included cases who had at least 1 year of follow-up to be able to adequately measure adherence in the primary analysis. Therefore, stroke cases occurring in the first year of treatment were excluded, which could introduce selection bias. However, we also excluded controls with <1 year of follow-up and in the sensitivity analysis including cases and controls that had at least 182 days of follow-up, we found similar associations.

In conclusion, we found that both persistence and adherence rates were high in the Stockholm region compared to previously published data, even with longer follow-up. Both persistence and adherence increased in more recent years with the NOACs having been longer on the market. This gradual improvement rather than deterioration of drug-taking behaviour is important, as there are clear associations

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between persistence or the level of adherence and stroke risk. Interventions aimed at further improving persistence and adherence should be encouraged, as the protective effect of NOACs disappeared with non-persistence and at low adherences rates.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

Ethical approval

The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2).

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Conflict of interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any additional organization for the submitted work. J.J.K. reports personal fees from Boehringer Ingelheim, outside the submitted work; O.H.K. reports grants from GSK and Lygature; personal fees from Roche, outside the submitted work. And all other authors have no conflict of interest to declare.

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