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**CLINICAL RESEARCH**
*Atrial fibrillation*

# Persistence and adherence to non-vitamin K antagonist oral anticoagulant treatment in patients with atrial fibrillation across five Western European countries

**Joris J. Komen [1,2]*, Anton Pottegård[3], Aukje K. Mantel-Teeuwisse[1], Tomas Forslund [2,4], Paul Hjemdahl [4], Björn Wettermark[5], Maja Hellfritzsch[3,6], Jesper Hallas [3], Morten Olesen[3], Marion Bennie[7,8], Tanja Mueller[7], Annemarie Voss[9], Tania Schink[9], Ulrike Haug[9,10], Bianca Kollhorst[11], Øystein Karlstad[12], Lars J. Kjerpeseth[12], and Olaf H. Klungel[1,3]***

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Healthcare Development, Stockholm Region, Public Healthcare Services Committee, Stockholm, Sweden; [3]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark; [4]Department of Medicine Solna, Clinical Epidemiology/Clinical Pharmacology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [5]Department of Pharmacy, Pharmacoepidemiology & Social Pharmacy, Uppsala University, Uppsala, Sweden; [6]Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark; [7]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK; [8]Public Health and Intelligence Strategic Business Unit, NHS National Services Scotland, Glasgow, UK; [9]Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany; [10]Faculty of Human and Life Sciences, University of Bremen, Bremen, Germany; [11]Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany; and [12]Chronic Diseases and Ageing, Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

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**Aims** To assess persistence and adherence to non-vitamin K antagonist oral anticoagulant (NOAC) treatment in patients with atrial fibrillation (AF) in five Western European healthcare settings.

**Methods and results** We conducted a multi-country observational cohort study, including 559 445 AF patients initiating NOAC therapy from Stockholm (Sweden), Denmark, Scotland, Norway, and Germany between 2011 and 2018. Patients were followed from their first prescription until they switched to a vitamin K antagonist, emigrated, died, or the end of follow-up. We measured persistence and adherence over time and defined adequate adherence as medication possession rate ≥90% among persistent patients only.

**Results** Overall, persistence declined to 82% after 1 year and to 63% after 5 years. When including restarters of NOAC treatment, 85% of the patients were treated with NOACs after 5 years. The proportion of patients with adequate adherence remained above 80% throughout follow-up. Persistence and adherence were similar between countries and was higher in patients starting treatment in later years. Both first year persistence and adherence were lower with dabigatran (persistence: 77%, adherence: 65%) compared with apixaban (86% and 75%) and rivaroxaban (83% and 75%) and were statistically lower after adjusting for patient characteristics. Adherence and persistence with dabigatran remained lower throughout follow-up.

* Corresponding authors. Tel: +31 0 30 253 7324; fax: +31 0 30 253 9166. *E-mail address*: J.J.Komen@uu.nl (J.K.); Tel: +31 0 30 253 7324; fax: +31 0 30 253 9166. *E-mail address*: O.H.Klungel@uu.nl

**Conclusion** Persistence and adherence were high among NOAC users in five Western European healthcare settings and increased in later years. Dabigatran use was associated with slightly lower persistence and adherence compared with apixaban and rivaroxaban.

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

## What's new?

- In five Western European countries, including 559 445 patients with atrial fibrillation started on a NOAC, persistence and adherence were high through 5 years of follow-up.
- Persistence declined to 82% after 1 year and to 63% after 5 years and over 80% of the patients had adequate adherence during follow-up.
- Both persistence and adherence were higher in patients starting treatment in later years.
- Both persistence and adherence were lower with dabigatran compared with apixaban and rivaroxaban, after adjusting for patient characteristics.

# Introduction

To prevent stroke in patients with non-valvular atrial fibrillation (AF), non-vitamin K antagonist oral anticoagulants (NOACs) are recommended as first line antithrombotic treatment.[1] Randomized clinical trials have shown comparable efficacy and safety profiles of NOACs compared with vitamin K antagonists (VKAs),[2] but, among other advantages, NOACs do not require regular monitoring of their anticoagulative effect. The lack of regular monitoring, as is required with VKAs, has led to concerns about lower persistence and adherence with NOACs than with VKAs.[1] Thus, guidelines stress the importance of active promotion of adherence and persistence in patients on NOAC treatment by discussing these issues with patients.

Several single-centre studies have assessed the persistence and adherence to NOAC treatment.[3] Persistence refers to whether a patient continues treatment after initiation, while adherence refers to whether a patient takes the treatment as prescribed.[4] Currently reported results on persistence and adherence to NOAC treatment vary considerably; a recent systematic review, based on 23 publications, reports persistence after 12 months ranging from 45% to 88%, and adherence in the first 6 months ranging from 48% to 92%.[3]

Comparisons of results from different studies on adherence and persistence are challenged by variations in essential definitions, e.g. for treatment discontinuation. Furthermore, studies vary in how they measure adherence and handle stockpiling. As such, large-scale studies applying a consistent methodology to estimate adherence and persistence across different healthcare settings, thereby generating comparable and generalizable data, are warranted. In addition, most persistence and adherence studies were conducted shortly after the NOACs were introduced to the market, and studies showing how persistence and adherence have evolved over time are scarce.

Being able to adequately describe adherence and persistence with different NOACs is important for both clinicians and policy makers in order to show where efforts are warranted to improve treatment, especially since large-scale studies comparing the different NOACs are lacking. Adequate adherence and persistence with NOACs for stroke prevention is essential, as shown by two recent publications in which adherence above 90% gave optimal stroke prevention, while both non-persistence and lower adherence were associated with two-fold increases in the risk of stroke.[6,7] This makes the comparison of persistence and adherence between NOACs an essential aspect of the overall relative comparative effectiveness in this drug class.

Therefore, the aim of the current study was to assess persistence and adherence with NOAC treatment, overall and by specific drug, in patients with AF using large healthcare databases from five Western European healthcare settings.

# Methods

## Setting

We analysed data from five Western European healthcare settings: Denmark, Norway, Scotland, Germany, and the Stockholm Region in Sweden. All data sources are described in detail elsewhere and an overview is provided in Supplementary material online, *Appendix Table S1*. In short, each data source contains data on dispensed prescriptions and secondary care diagnoses, except for Germany where there is no distinction between primary and secondary care, but only between inpatient and outpatient care, which are both captured in the data source (see Supplementary material online, *AppendixTable S1*). Data from Stockholm also include diagnoses from primary care. The data from Stockholm, Denmark, Norway, and Scotland cover unselected populations from an entire region/country, while the data from Germany cover unselected populations from four statutory health insurances in Germany (~20% of the German population overall).

## Patient selection

Patients were included in the cohort when they claimed their first prescription of a NOAC, after a washout period of 1 year, between April 2011 (European Medicine's Agency approval date for dabigatran) and the end of data availability (2018 for Stockholm, Denmark, and Norway; 2017 for Scotland and Germany). The first prescription claim date was considered the index date (see Supplementary material online, *Appendix Figure S1*). We only included patients with a recorded diagnosis of AF prior to or on the date of their first NOAC claim. Patients assumed to use their NOAC for other reasons than AF were excluded. Specifically, we excluded patients with a diagnosis of deep venous thromboembolism or pulmonary embolism or a procedure code for knee/hip replacement surgery in the 30 days before and after the index date, or for whom a prescription was linked to these procedures (for Norway only). We followed patients until they claimed a VKA prescription, died, moved out of

the country/region, reached the end of data availability, or reached the maximum follow-up time of 5 years.

We measured the baseline medication use in the six months prior to index date, and comorbidities in the 5 years prior to index date. For baseline medication, we searched for prescriptions of VKA, low-dose aspirin, P2Y12-inhibitors, NSAIDs, corticosteroids, diuretics, beta-blockers, calcium channel blockers, renin–angiotensin–aldosterone system (RAAS) inhibitors, statins, oral antidiabetics, insulin, and antidepressants. For comorbidities, we searched for components of the $CHA_2DS_2$-VASc and modified HAS-BLED scores (without labile INR): heart failure, hypertension, prior stroke/TIA/embolism, vascular disease, diabetes; renal disease, liver disease, prior bleed, anaemia, and alcohol abuse.

Follow-up time was partitioned into six-month intervals, and persistence and adherence were calculated for each interval in patients for which data were available in the specific interval. In the first years of treatment, we partitioned the follow-up time into 3-month intervals, as changes in persistence and adherence are common during the first year of treatment.

## Persistence

We considered patients to be persistent (i.e. continuing the treatment) when they claimed a NOAC prescription within 91 days after the end of the estimated duration of a prior prescription (see Supplementary material online, *Appendix Figure S1*). We calculated the duration of a prescription by dividing the quantity dispensed by the recommended dose for each NOAC (once daily for rivaroxaban and edoxaban, twice daily for dabigatran and apixaban). In addition, if patients had tablets/capsules of the same NOAC available from prior prescriptions (i.e. stockpiling), we added those to the supply of a following prescription, with a maximum of 61 days added to a prescription.[8] If a patient claimed a different NOAC during follow-up than the NOAC the patient started with, we considered the patient to be on continued NOAC treatment with the initially started NOAC (intention to treat analysis). If a patient switched, potential stockpiling from prior prescriptions was disregarded, and we assumed the patient started with the new prescription on the first day of claiming it. If a patient failed to reclaim a NOAC prescription within the given limits, we considered the patient to be non-persistent. The date of non-persistence was set at the calculated end of the last prescription plus a permissible gap of 91 days. We calculated the proportion of patients in the cohort that was persistent on the first day of each follow-up interval.

Besides persistence, we also measured the proportion of patients in the cohort on treatment on the first day of each follow-up interval to obtain treatment coverage.[9] Using this approach, we also captured patients who restarted NOAC treatment after having stopped the treatment for a while, as discontinuation did not lead to censoring.

## Adherence

During the time a patient was persistent with the treatment, we calculated the adherence. Adherence was only measured in persistent patients as it cannot meaningfully be calculated in non-persistent patients. We used the medication possession rate (MPR) to quantify adherence.[8] The MPR was calculated by dividing the number of days in which a patient had the drug available by the number of days in each interval. Again, we took stockpiling from previous prescriptions into account. For each time-point during follow-up, we assessed the proportion of persistent patients with an MPR $\geq$ 90%. We chose the MPR cut-off of 90%, as adherence below 90% has been found to be associated with reduced stroke protection.[6,7]

## Persistence and adherence over time and across non-vitamin K antagonist oral anticoagulants

For each calendar-year of inclusion into the study, we measured the proportion of patients persistent after 1 year and the proportion of patients with an MPR $\geq$ 90% during their first year of treatment, to analyse if and how persistence and adherence changed over time. We excluded patients with a follow-up of <1 year for this analysis. We used the same approach to describe first-year persistence and adherence with the different NOACs. As edoxaban was only recently introduced to the market and had few users, we discarded edoxaban from this analysis.

## Statistical analysis

We used a common data model to analyse data from the databases available in the different centres (specifications from the common data model are available from the authors at request). All databases included comparable data, coded in a similar manner. Therefore, the common data model only required information on renaming variables. The same R-script for the generation of the analytical datasets and conduct of the statistical analyses was used in all databases, to ensure identical analyses in the different centres. The R-script was sent to all centres, and therefore all individual data stayed locally, and only the final results (descriptive characteristics, point estimates) left the centre.

We used descriptive statistics to describe the cohorts and persistence and adherence over time. To analyse whether first-year persistence and adequate first-year adherence (i.e. MPR $\geq$ 90%) differed between the NOACs, we used logistic regression. The dependent variable in the model was either persistence after 1 year or adequate adherence (i.e. MPR $\geq$ 90%) during the first year. We included the different NOACs as an independent categorical variable in the model with apixaban as the reference NOAC, and adjusted for age, sex, the aforementioned covariates on baseline medication and comorbidity, and year of inclusion. Using the same model, we also evaluated whether adherence and persistence changed over time. We excluded patients initiated on edoxaban from these analyses due to small sample size.

All statistical analyses were performed with the statistical software R. We used the 'AdhereR' package to create treatment episodes.

## Sensitivity analyses

There might be a lag in the recording of AF diagnoses, especially for databases with only secondary care data.[10] Therefore, we performed a sensitivity analysis in which we also included patients with an AF diagnosis in the 91 days after their first NOAC prescription, instead of only patients with an AF diagnosis prior to or on the date of the first NOAC prescription.

The Stockholm Healthcare database had access to both primary and secondary care data and this might result in a patient population different from the other data sources due to the additional data availability. To assess if this affected the results, we performed a sensitivity analysis in which we only included data from secondary care in Stockholm and compared this with the main analysis from Stockholm with both primary and secondary care data.

# Results

In total, we included 555 943 patients claiming a first NOAC. The largest cohort ($n$ = 290 043) was from the German database and the smallest ($n$ = 34 837) was from the Stockholm database (*Table 1* and Supplementary material online, *Table S2*). The median follow-up was

**Table 1 Summary of baseline characteristics of patients included per database**

| | Stockholm | Denmark | Scotland | Norway | Germany |
|---|---|---|---|---|---|
| Number of patients | 34 837 | 97 077 | 35 934 | 98 052 | 290 043 |
| Female (%) | 15 725 (45.1%) | 43 804 (45.1%) | 17 015 (47.4%) | 41 057 (41.9%) | 139 121 (48.0%) |
| Age | | | | | |
| Years, mean (SD) | 74.64 (11.00) | 74.75 (11.07) | 75.15 (10.94) | 74.74 (10.82) | 74.44 (10.68) |
| 0–64 | 5492 (15.8%) | 15 717 (16.2%) | 5586 (15.5%) | 15 172 (15.5%) | 47 257 (16.3%) |
| 65–74 | 11 242 (32.3%) | 30 259 (31.2%) | 9677 (26.9%) | 31 574 (32.2%) | 80 166 (27.6%) |
| 75–84 | 11 267 (32.3%) | 31 439 (32.4%) | 13 478 (37.5%) | 31 883 (32.5%) | 115 180 (39.7%) |
| ≥85 | 6836 (19.6%) | 19 662 (20.3%) | 7193 (20.0%) | 19 423 (19.8%) | 47 440 (16.4%) |
| Baseline treatment | | | | | |
| VKA | 10 188 (29.2%) | 27 011 (27.8%) | 12 819 (35.7%) | 26 304 (26.8%) | 59 185 (20.4%) |
| Aspirin | 9528 (27.4%) | 28 241 (29.1%) | 11 071 (30.8%) | 35 840 (36.6%) | 33 401 (11.5%) |
| NOAC of inclusion | | | | | |
| Apixaban | 23 547 (67.6%) | 33 447 (34.5%) | 20 932 (58.3%) | 51 754 (52.8%) | 88 275 (30.4%) |
| Dabigatran | 6301 (18.1%) | 28 025 (28.9%) | 1449 (4.0%) | 20 387 (20.8%) | 38 860 (13.4%) |
| Edoxaban | 98 (0.3%) | 1746 (1.8%) | 78 (0.2%) | 752 (0.8%) | 14 552 (5.0%) |
| Rivaroxaban | 4891 (14.0%) | 33 859 (34.9%) | 13 475 (37.5%) | 25 159 (25.7%) | 148 356 (51.1%) |
| $CHA_2DS_2$-VASc | | | | | |
| Mean (SD) | 3.10 (1.80) | 2.94 (1.67) | 3.20 (1.74) | 2.96 (1.66) | 3.70 (1.93) |
| 0 | 2041 (5.9%) | 5726 (5.9%) | 1937 (5.4%) | 5644 (5.8%) | 11 855 (4.1%) |
| 1 | 4713 (13.5%) | 13 272 (13.7%) | 4030 (11.2%) | 12 986 (13.2%) | 26 267 (9.1%) |
| 2–4 | 20 513 (58.9%) | 61 130 (62.8%) | 21 769 (60.6%) | 62 156 (63.4%) | 152 306 (52.5%) |
| ≥5 | 7570 (21.7%) | 16 949 (17.5%) | 8193 (22.8%) | 17 266 (17.6%) | 99 615 (34.3%) |
| HAS-BLED | | | | | |
| Mean (SD) | 1.96 (1.13) | 1.90 (1.11) | 2.06 (1.14) | 1.95 (1.10) | 2.37 (1.31) |
| 0 | 2659 (7.6%) | 7655 (7.9%) | 2290 (6.4%) | 6947 (7.1%) | 16 636 (5.7%) |
| 1–2 | 21 738 (62.4%) | 63 133 (65.0%) | 22 015 (61.3%) | 63 233 (64.5) | 146 916 (50.7%) |
| ≥3 | 10 440 (30.0%) | 26 288 (27.1%) | 11 624 (32.3%) | 27 872 (28.4%) | 126 491 (43.6%) |

Full baseline characteristics with all comorbidities and comedication can be found in Supplementary material online, *Appendix Table S1*.
NOAC, non-vitamin K antagonist oral anticoagulant; SD, standard deviation; VKA, vitamin K antagonist.

>1 year (data not shown), there were fewer female than male patients, and the mean age was ∼75 years in all countries. In Stockholm, Scotland, and Norway, apixaban was prescribed to >50% of the new NOAC users. The proportion of patients initiated with dabigatran varied markedly, from 4% in Scotland to 29% in Denmark. In Germany, most patients were initiated on rivaroxaban (51% of all first prescriptions), while in Denmark, there was no clearly preferred NOAC. Edoxaban comprised a small proportion of all prescriptions across all countries (≤5%). During follow-up, 8.0% of the patients switched to warfarin and were censored from further analysis. Switchers to warfarin decreased from 21.9% of all patients initiated on a NOAC in 2011 to 1.4% in 2018.

The stroke risk according to $CHA_2DS_2$-VASc was similar in all countries. The mean $CHA_2DS_2$-VASc score ranged from 2.9 in Denmark to 3.7 in Germany, and >50% of the patients had a $CHA_2DS_2$-VASc score between 2 and 4 in all countries. The bleeding risk according to modified HAS-BLED scores ranged from 1.9 in Denmark to 2.4 in Germany, and >50% of the patients had HAS-BLED scores of 1–2 in all countries (*Table 1*). Approximately 30% claimed a VKA and 30% claimed aspirin in the 6 months prior to index date in all countries except for Germany, where only 20% had claimed a VKA and 12% aspirin.

Persistence declined steadily to 82% after 1 year and 63% after 5 years, in patients for whom data were available (*Figure 1A*). Among patients who were persistent, >75% had an MPR ≥90% which remained stable from 1 year of follow-up onwards (*Figure 1B*). The rate declined sharply and moved back up in the beginning of follow-up, as non-persistence and non-adherence can overlap during that period. The proportion of patients treated with a NOAC, i.e. all patients classified as on therapy at the beginning of a given time period and thus including restarts, dropped to 85% after 1 year and remained stable at that level (*Figure 1C*).

The proportion of patients that was persistent after 1 year of treatment increased in later calendar years (*Figure 2A*). Among patients initiating in 2011, 76% were on treatment after 1 year and this steadily increased to 84% of patients initiating in 2016 (and 87% in 2017, without data from Germany and Scotland). Results from logistic regression showed this gradual increase was statistically significant and independent of changes in baseline characteristics; there were significant increases in 1-year persistence per calendar year in four of the five countries (*Table 2*). Only in Stockholm, where the proportion was already 87% in 2011, there was no further increase. The proportion of patients with adequate adherence (MPR ≥ 90%) during the first year of treatment increased from 62% in 2011 to 75% in 2016

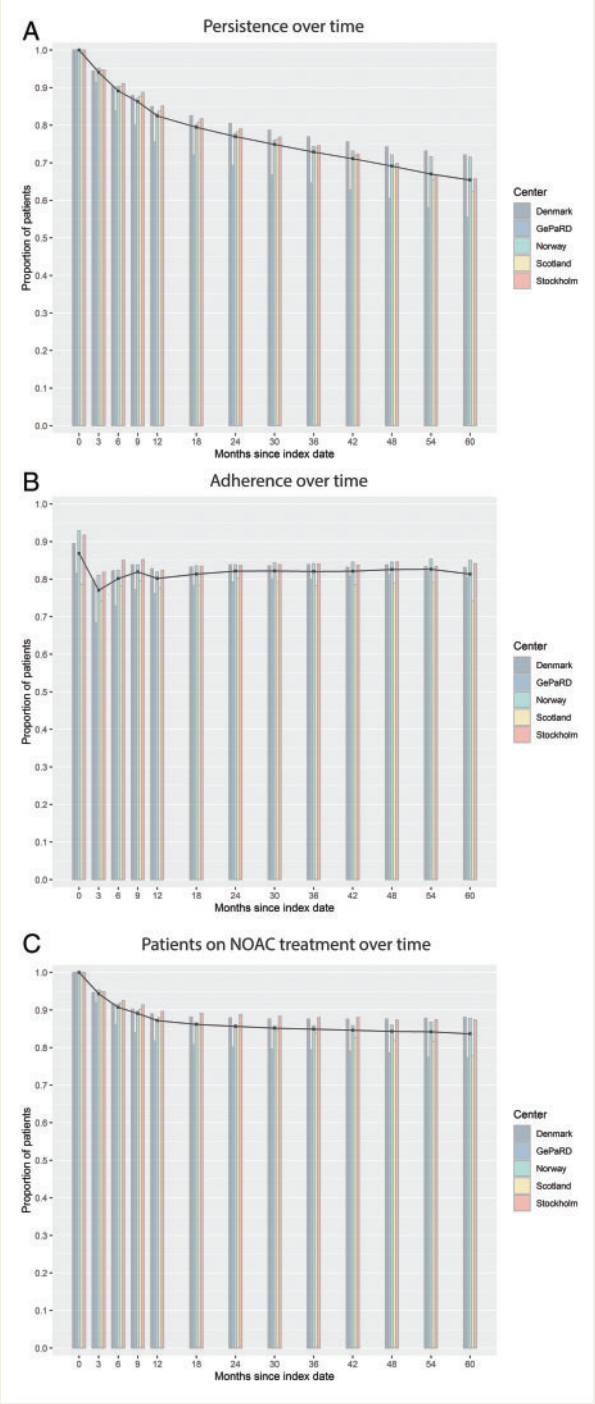


**Figure 1** (*A*) Proportion of persistent patients during follow-up overall and per country. The line is the average persistence in the five countries. The values on the *x*-axis represent the start of an interval. (*B*) Proportion of patients with an adequate adherence (i.e. MPR ≥ 90%) during follow-up overall and per country. The line is the average proportion in the five countries. The values on the *x*-axis represent the start of an interval. (*C*) Proportion of patients on NOAC treatment, including restarts, during follow-up overall and per country. The line is the average proportion of the five countries. The values on the *x*-axis represent the start of an interval. MPR, medication possession rate; NOAC, non-vitamin K antagonist oral anticoagulant.

(and 80% in 2017, without data from Germany and Scotland, *Figure 2B*). Again, the increase was statistically significant in all regions except Stockholm, where the rate was 81% in 2011 already.

The mean first-year persistence was 79% for dabigatran, 84% for rivaroxaban, and 86% for apixaban, and persistence continued to be highest with apixaban and lowest with dabigatran throughout follow-up (*Figure 3A*). After adjusting for covariates, apixaban was associated with a significantly higher 1-year persistence than both rivaroxaban and dabigatran in all countries except Norway where there was no difference between apixaban and rivaroxaban (*Table 2*). The mean first-year adherence (MPR ≥ 90%) was 65% with dabigatran, 75% with apixaban, and 76% with rivaroxaban, and was highest for rivaroxaban and lowest for dabigatran throughout follow-up (*Figure 3B*). Apixaban and rivaroxaban use was associated with higher first-year adherence compared with dabigatran in all countries except Germany where there was no difference between rivaroxaban and dabigatran. Rivaroxaban use was associated with higher first-year adherence compared with apixaban in Denmark, Norway, and Germany, while in Stockholm rivaroxaban use was associated with lower adherence than apixaban, and in Scotland this association was neutral (*Table 2*). The lower adherence and persistence with dabigatran remained after stratifying on year of inclusion (Supplementary material online, *Appendix Figures S2 and S3*).

Including patients with an AF diagnosis registered during the first 91 days after NOAC initiation led to a higher number of patients included; the increase was largest in Denmark with 11% more patients, and smallest in Norway with only 1% more patients. Baseline characteristics and persistence were similar when using this extended patient selection (Supplementary material online, *Table S3*). Restricting the Stockholm data to only secondary care yielded 4349 fewer patients (−12%) but had no impact on baseline characteristics or estimates of persistence.

## Discussion

In this large cross-national population-based cohort study of 559 445 European AF patients on NOAC treatment, we found that both persistence and adherence were high. When taking restarters of treatment into account, >80% of patients remained on treatment throughout 5 years of follow-up. Both persistence and adherence during the first year of treatment increased in later years, independently of changing baseline covariates. Early discontinuation of NOAC therapy was more common among dabigatran and rivaroxaban users compared with apixaban users. In persistent patients, 80% of them had an MPR ≥90% during follow-up. When comparing adherence with the different NOACs, dabigatran had the lowest MPR in all countries and rivaroxaban performed slightly better than apixaban, although this was not visible in all five countries.

Comparing the different NOACs after adjustment for baseline characteristics, we found both lower persistence and adherence with dabigatran compared with the other two NOACs. This is in line with randomized trial data, showing that persistence with apixaban and rivaroxaban was comparable with warfarin after ∼2 years, but the rates were statistically lower when comparing dabigatran with warfarin (79% vs. 83%).[11–13] Some factors that could explain the lower persistence with dabigatran are, first, dyspepsia, a known side effect

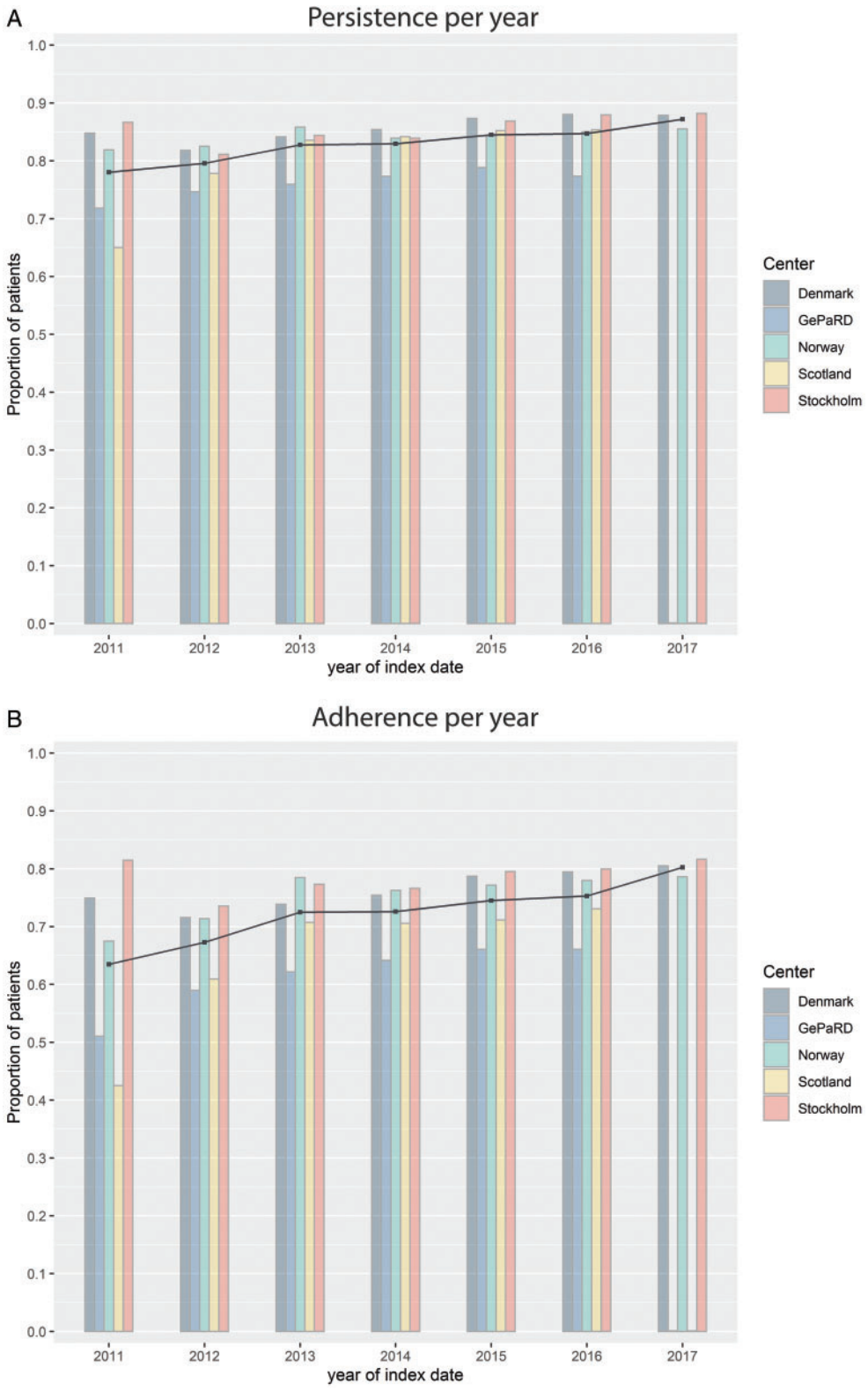


**Figure 2** (*A*) Proportion of patients with at least 1 year of follow-up who were persistent after 1 year of follow-up per calendar year per country. The line is the average proportion in the five countries. (*B*) Proportion of patients with at least 1 year of follow-up who had a medication possession rate > 90% in their first year of follow-up per calendar year per country. The line is the average proportion from the five countries.

**Table 2 Proportion of patients that were persistent or adequately adherent in their first year of treatment, and results from the logistic regression**

| | Persistent after 1 year | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Apixaban** | **Dabigatran** | **Rivaroxaban** | **Dabi:apix** | **Riva:apix** | **Dabi:riva** | **Year increase** |
| Stockholm | 0.89 | 0.80 | 0.85 | 0.56 (0.50–0.63) | 0.66 (0.59–0.74) | 1.24 (1.11–1.37) | 1.01 (0.97–1.04) |
| Denmark | 0.89 | 0.83 | 0.87 | 0.72 (0.67–0.77) | 0.88 (0.83–0.94) | 1.43 (1.36–1.52) | 1.07 (1.05–1.09) |
| Scotland | 0.87 | 0.75 | 0.83 | 0.44 (0.37–0.52) | 0.71 (0.65–0.77) | 1.75 (1.52–2.01) | 1.04 (1.01–1.08) |
| Norway | 0.85 | 0.82 | 0.86 | 0.80 (0.75–0.85) | 1.00 (0.95–1.06) | 1.53 (1.45–1.61) | 1.04 (1.02–1.05) |
| Germany | 0.80 | 0.76 | 0.76 | 0.89 (0.86–0.93) | 0.91 (0.89–0.94) | 1.38 (1.34–1.42) | 1.09 (1.08–1.10) |
| Overall | 0.86 | 0.79 | 0.84 | N/A | N/A | N/A | N/A |
| | **MPR > 90% in first year** | | | | | | |
| | **Apixaban** | **Dabigatran** | **Rivaroxaban** | **Dabi:apix** | **Riva:apix** | **Dabi:riva** | **Year increase** |
| Stockholm | 0.82 | 0.73 | 0.79 | 0.68 (0.62–0.75) | 0.84 (0.77–0.93) | 1.17 (1.04–1.32) | 1.02 (0.99–1.04) |
| Denmark | 0.79 | 0.72 | 0.80 | 0.78 (0.74–0.83) | 1.12 (1.06–1.18) | 1.23 (1.15–1.32) | 1.06 (1.04–1.07) |
| Scotland | 0.72 | 0.57 | 0.72 | 0.60 (0.52–0.69) | 1.04 (0.97–1.11) | 1.62 (1.38–1.90) | 1.08 (1.05–1.11) |
| Norway | 0.78 | 0.73 | 0.81 | 0.79 (0.75–0.84) | 1.21 (1.15–1.27) | 1.25 (1.18–1.33) | 1.05 (1.03–1.07) |
| Germany | 0.64 | 0.57 | 0.65 | 0.87 (0.84–0.90) | 1.20 (1.17–1.23) | 1.02 (0.99–1.06) | 1.12 (1.11–1.13) |
| Overall | 0.75 | 0.66 | 0.76 | N/A | N/A | N/A | N/A |

The first three columns represent the crude proportion of patients that were persistent or adherent in their first year of treatment, per country. The last three columns show the odds ratios and 95% confidence intervals of being persistent or adherent comparing dabigatran to apixaban, comparing rivaroxaban to apixaban, and per increasing calendar year of index date. The logistic regression model was adjusted for age, sex, baseline comedication, and comorbidities and year of inclusion. We removed edoxaban from this analysis, given the limited sample size.

of dabigatran and a cause for treatment discontinuation.[14] Second, dabigatran was the first approved NOAC for use during cardioversion and ablation,[15] which can be an indication for short term use. Finally, dabigatran cannot be repackaged to other dispensing systems, which are known to improve adherence.[16]

Persistence and adherence were both high. At the end of follow-up, ~63% of the patients were persistent with the initial treatment without a treatment break, but many patients resumed NOAC treatment after a break and >80% were actually NOAC treated during the follow-up. In persistent patients, 20% of them had inadequate adherence with an MPR <90%. Previous work has shown that both non-persistence and inadequate adherence are associated with two-fold increases in the risk for stroke.[7] Therefore, additional efforts are needed to optimize these important aspects of treatment, especially in patients initiated on dabigatran.[17]

In this study, we did not assess outcomes associated with either persistence or adherence. The meta-analysis by Simpson *et al.*[18] showed a significantly lower mortality-risk in patients that were adherent to placebo therapy, supporting the existence of a 'healthy adherer' effect. This makes it complicated to study the effects of adherence/persistence on mortality and we believe that these results will not likely be fully valid. Especially in an already complicated multi-database cross-country setting as in the current study.

Our study has several strengths. First, this is, to our knowledge, the first multi-country persistence and adherence study using a common protocol, a common data model, and centrally developed programming scripts. This makes it possible to obtain valid comparisons between countries as the comparability is not influenced by study design, analytical choices, or variation in programming. This is especially important in persistence and adherence studies, as there are numerous ways to measure these parameters, which can influence study results considerably.[4,8] Secondly, we used data from five Western European healthcare systems and found consistent results, making our results generalizable to other countries with similar healthcare systems. Thirdly, we examined adherence and persistence separately, as they are two different phenomena. Without distinction between them, adherence will be underestimated among patients who stopped treatment and they will inadvertently have extremely low adherence. In addition, we used advanced methods to measure persistence and adherence, taking stockpiling from previous prescriptions into account.

## Limitations

Our study has some limitations. First, our study relied on pharmacy claims data, assuming that patients claiming their prescriptions are truly taking the treatment, which may not always be the case. However, if patients do not redeem new prescriptions, it is very likely that they have indeed stopped treatment. The same goes for adherence; if a patient claims too little of the medication within a given timespan, it is very unlikely the patient is taking the drug as prescribed. In addition, there may be some differences amongst countries in prescription regulations and reimbursement systems, as well as coding practices. Secondly, the prevalence of diseases may partly have been over- or under-estimated. Especially in Germany, where algorithms with a high sensitivity, but a low specificity were used to assess comorbidities, which could explain the higher overall comorbidity prevalence in Germany. Thirdly, we did not have data on reasons for discontinuation. In some instances, a severe bleed can be a

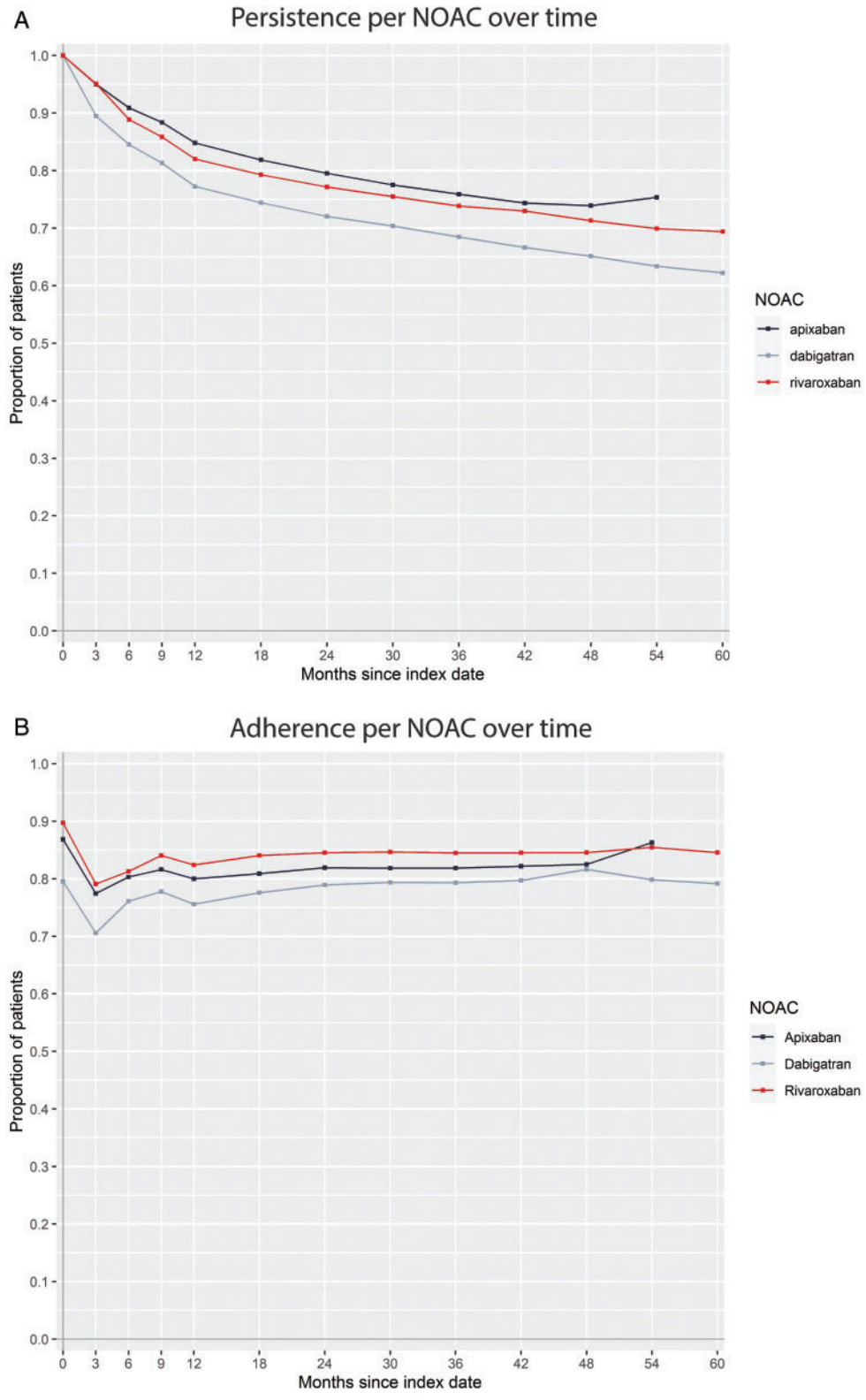


**Figure 3** (*A*) Proportion of persistent patients during follow-up per NOAC. Patients initiated on edoxaban were excluded given the limited sample size. (*B*) Proportion of patients with a medication possession rate > 90% during follow-up per NOAC. Patients initiated on edoxaban were excluded given the limited sample size. NOAC, non-vitamin K antagonist oral anticoagulant.

reason for treatment discontinuation.[1,19] Prior work from Denmark and Stockholm has shown that 7.6% and 6.5% of the patients stopping treatment suffered a severe bleed.[7,20] Fourthly, we censored patients when they claimed a VKA prescription, therefore we have no data on whether patients actually continued treatment with an oral anticoagulant after a switch. Fifthly, we did not have access to data that may indicate transient use of NOAC therapy, for example, cardioversion or catheter ablation, in all databases.

# Conclusion

In more than half a million AF patients initiated on NOAC therapy from five Western European healthcare settings, both adherence and persistence were high and increasing in later years, which is important given the increased risk for stroke associated with non-persistence and poor adherence. Dabigatran users had lower persistence and adherence compared with apixaban and rivaroxaban users, after taking baseline characteristics into account. This finding indicates a need for additional monitoring and efforts to remain on treatment in patients initiated on dabigatran.

# Supplementary material

Supplementary material is available at *Europace* online.

**Conflict of interest:** J.K. reports personal fees from Boehringer Ingelheim; A.P. reports grants from Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, and LEO Pharma, outside the submitted work; A.V., T.S., U.H., and B.K. report that they are working at the Leibniz Institute for Prevention Research and Epidemiology—BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry; Ø.K. reports participation in imposed Post-Authorization Safety Studies on an antidiabetic and an anti-psoriasis drug. The studies are funded by Leo Pharma and Novo Nordisk, with funds paid to the institution where he is employed (no personal fees) and with no relation to the work reported in this article. All other authors have nothing to declare.

## Data availability

Ethical regulations prohibit sharing of data.

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