Switching from vitamin K antagonists to direct oral anticoagulants in non-valvular atrial fibrillation patients: does low time in therapeutic range affect persistence?

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ORIGINAL ARTICLE

Switching from vitamin K antagonists to direct oral anticoagulants in non-valvular atrial fibrillation patients: Does low time in therapeutic range affect persistence?

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Abstract

Background: Non-valvular atrial fibrillation (NVAF) patients are advised to switch from a vitamin K antagonist (VKA) to direct oral anticoagulant (DOAC) when time in therapeutic range (TTR) is low.

Objective: To examine if pre-switch TTR determines persistence patterns in NVAF patients who are switched from a VKA to DOAC.

Patients/Methods: Adult NVAF patients from three Dutch anticoagulation clinics who were newly switched from a VKA to DOAC between July 1, 2013 and September 30, 2018 were stratified by pre-switch TTR levels. DOAC prescription records were examined to determine persistence patterns according to a 100-day prescription gap. Cumulative incidences of non-persistence to DOAC were estimated using the cumulative incidence competing risk method. The association of pre-switch TTR levels with DOAC non-persistence was evaluated by Cox regression models.

Results: A total of 3696 NVAF patients were included, of whom 690 (18.7%) had a pre-switch TTR ≤ 45%. After switching from VKA to DOAC, 14.0% (95% confidence interval [CI] 11.3–17.0%) of the patients with a pre-switch TTR ≤ 45% became non-persistent to DOAC within 1 year, while 9.8% (95% CI 8.7–11.0%) did in those with a pre-switch TTR > 45%. In a multivariable model, a pre-switch TTR ≤ 45% was associated with a higher risk of non-persistence to DOAC (adjusted hazard ratio 1.55, 95% CI 1.22–1.97). Results were similar when using other cut-off points (60% or 70%) to define a low TTR.

Conclusion: NVAF patients switching from VKA to DOAC due to a low pre-switch TTR saw a worse persistence pattern to DOAC after the switch compared to patients with a high pre-switch TTR.

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KEYWORDS
atrial fibrillation, coumarins, direct-acting oral anticoagulant, medication persistence, quality control

1 | INTRODUCTION

Non-valvular atrial fibrillation (NVAF), which is associated with a 5-fold increased risk of ischemic stroke, is a prevalent burden of disease worldwide.[1] To prevent ischemic stroke, the use of a long-term oral anticoagulant (OAC) is recommended for patients with a high ischemic stroke risk.[2] For many years, a vitamin K antagonist (VKA) was the main oral therapeutic option for long-term anticoagulant treatment.[3] Patients using VKAs require regular laboratory monitoring and subsequent dose adjustments based on the international normalized ratio (INR), due to a small therapeutic window and frequent interactions between VKAs and co-medication or diet.[4,5] The quality of VKA therapy can be evaluated by calculating the time in therapeutic range (TTR) using the Rosendaal method,[6] of which a TTR > 70% is considered a good quality of VKA therapy.[2] A low TTR is associated with an increased risk of ischemic stroke.[7,8] Therefore, the following interventions for patients with a low TTR are recommended: (a) more frequent INR monitoring and patient education or, (b) switching to a direct oral anticoagulant (DOAC).[2] From 2011 onward, DOACs were introduced for NVAF and were found non-inferior to VKAs in several large randomized clinical trials.[9,10] As opposed to VKAs, DOACs do not require frequent laboratory monitoring. The lack of monitoring, however, may contribute to suboptimal treatment persistence to DOACs, which was identified by several observational studies.[11-14]

Although NVAF patients who receive VKAs but with a low TTR are suggested to switch to a DOAC,[2] it is unknown whether the switch improves the persistence to oral anticoagulation. This question is relevant because non-persistence to OAC was associated with an increased risk of ischemic stroke in DOAC users.[14,15] For this reason, we conducted a cohort study that included NVAF patients from three Dutch anticoagulation clinics who were newly switched from a VKA to a DOAC between 2013 and 2018, and examined persistence patterns to the DOAC between those with a low and a high pre-switch TTR level.

Essentials

- Non-valvular atrial fibrillation (NVAF) patients receiving a vitamin K antagonist (VKA) with low time in therapeutic range (TTR) are advised to switch to a direct oral anticoagulants (DOAC), but little is known about their persistence to DOACs.
- Former VKA patients from three Dutch anticoagulation clinics were included.
- Cumulative incidences and associations between TTR groups and DOAC non-persistence were estimated.
- Low pre-switch TTR was associated with increased risk of non-persistence to DOACs.

2 | METHODS

2.1 | Data sources

The study obtained individual patient data from three large Dutch anticoagulation clinics (located in Amsterdam, Leiden, and Utrecht), which are managed by the Dutch Federation of Anticoagulation Clinics ("Federatie Nederlandse Trombosediensten" [FNT]). These clinics monitor the VKA therapy of patients living in well-defined geographical areas. When enlisted by an anticoagulation clinic, several patient characteristics are registered, including date of birth, sex, co-medication, indication for VKA treatment, the start and end date of VKA treatment, and therapeutic range of INR. To monitor INR, appointments are made at least once every 6 weeks. The time interval between INR measurements depends on the stability of the INR. At each appointment, a standardized short questionnaire is used (and electronically stored) to document changes in co-medication, the onset of comorbidities, the occurrence of bleeding events, or scheduled invasive procedures (e.g., planned surgery or dental extractions).[16] In the study, the data we obtained were extracted on June 19, 2020.

The data from the three anticoagulation clinics were then linked at an individual level to the nationwide individual data (available from 2010 to 2018) from Statistics Netherlands ("Centraal Bureau voor de Statistiek" [CBS]). The gathering and linking of data by CBS have been described earlier,[14] and to ensure privacy, all data were deidentified, and a unique artificial personal identifier was assigned to each linked individual. In brief, the following data were used in the study: (a) data on personal characteristics and socioeconomic status from the Personal Records Database; (b) diagnosis data as listed during hospital admission from the National Basic Register of Hospital Care of Dutch Hospital Data, which includes all general and academic Dutch hospitals and two short-stay categorical hospitals (i.e., a cancer clinic and an eye hospital); (c) medication prescription data, for which the Dutch basic health insurance reimburses the costs (except for medication received in hospitals and nursing homes) collected from the Health Care Insurance Board. For VKA and DOAC prescription data, only the prescription dates and general types (i.e., DOAC or VKA) were available, while the amount of medication collected for each prescription, as well as DOAC or VKA subtypes were unavailable.

Anatomical Therapeutic Chemical (ATC) codes of the World Health Organization were used for medication identifications.

International Classification of Diseases (ICD) codes were used for disease identification (ICD-9 for diagnoses made from 2010 to 2012, and ICD-10 for diagnoses made from 2013 onward). All codes and variables used in this study are presented in Table S1 in supporting information. The study received ethical approval from the science committee of the FNT with a waiver of participant consent due to the use of pre-existing, de-identified data only.

2.2 | Study population

The study population consisted of a cohort of adult NVAF patients who were managed by one of the three anticoagulation clinics in the Netherlands and newly switched from VKA to DOAC between July 1, 2013 and September 30, 2018. In detail, adult (≥18 years) patients who were receiving a VKA and managed by a participating anticoagulation clinic with at least one available INR measurement between January 1, 2013 and June 19, 2020 were selected for consideration of inclusion in the study population. Those with at least one DOAC prescription (identified by ATC codes) between July 1, 2013 and September 30, 2018 were eligible. To ensure a follow-up time of at least 100 days (for the determination of persistence patterns, see below), patients who first received a DOAC between October 1 and December 31 of 2018 were not included. We only included patients who received a VKA for the indication of NVAF. Diagnoses data were screened for valvular heart diseases, and patients with a diagnosis of rheumatic mitral stenosis or mechanical heart valves (as identified by ICD codes) before or within 1 month after the index date (i.e., the date of the first DOAC prescription between July 1, 2013 and September 30, 2018) were excluded. Patients were followed from the index date onward until September 30, 2018 or date of death, whichever came first.

To ensure a reliable calculation of the TTR, we only included patients with a history of VKA use for at least 6 months and with at least six INR measurements within 6 months before the index date. To ensure that the included patients had used VKA shortly before DOAC was initiated (i.e., the patient was a true switcher), patients without VKA treatment within 2 months before the index date were excluded from the study population. In addition, if the previous VKA treatment did not stop within 2 months after the index date (according to the recorded end date of VKA treatment), the patients were also excluded. Patients with a DOAC and VKA prescription on the same date were excluded from the study. Detailed selection of the study population is presented in Figure 1.

2.3 | Baseline characteristics

Baseline characteristics of the study population were collected on the index date, and were stratified by baseline (i.e., pre-switch) TTR levels. The following characteristics were studied: age; sex; CHA_2DS_2-VASc score;[17] HAS-BLED score;[18] and the following comorbidities (identified by screening diagnosis data within 3 years before the index date): chronic obstructive pulmonary disease, asthma, other chronic lung diseases, congestive heart failure, hypertension, myocardial infarction history, abnormal liver function, gastroesophageal reflux disease, peptic ulcer disease, abnormal renal function, anemia, coagulopathy, diabetes mellitus, thyroid disease, autoimmune disease, systemic connective tissue disorder, ischemic stroke/transient ischemic attack (TIA), Alzheimer's disease, Parkinson's disease, peripheral artery disease, venous thromboembolism, deep vein thrombosis, pulmonary embolism, arterial embolism and thrombosis, major bleeding history, and malignant tumor.

To calculate the CHA_2DS_2-VASc score at baseline, we used a method that was previously described.[14] In brief, diagnosis data were screened and the following diagnoses were identified within the 3 years before the index date: congestive heart failure, hypertension, diabetes mellitus, and vascular disease (i.e., peripheral artery disease, myocardial infarction, aortic plaque). To calculate the HAS-BLED score at baseline, medication prescription and diagnosis data were screened, and the following variables were determined (if present within 1 year before the index date): uncontrolled hypertension (i.e., receiving at least three classes of antihypertensive drugs at the same time), abnormal renal function, abnormal liver function, prior history of ischemic stroke, prior major bleeding, alcohol abuse, and antiplatelet agents or nonsteroidal anti-inflammatory drugs. All codes used for the calculation of these scores are presented in Table S1.

2.4 | Baseline TTR calculation

The TTR before the switch from a VKA to a DOAC (i.e., on the index date, referred to as baseline TTR) was identified as the exposure. Baseline TTR was calculated by the Rosendaal method[6] using all available INR measurement records (at least six INR measurement records according to our above inclusion criteria) within 6 months before the index date. In brief, the Rosendaal method calculates TTR using the frequency of INR measurements and their values, under the assumption that changes between sequential INR measurements are linear over time. For INR measurements between January 1, 2013 and January 1, 2016, target ranges of 2.0–3.5 and 2.5–4.0 for, respectively, low- and high-intensity anticoagulant treatment (which was determined by their treating physicians) were used for TTR calculation. For INR measurements after January 1, 2016, target ranges of 2.0–3.0 and 2.5–3.5 for, respectively, low- and high-intensity anticoagulant treatment were used for TTR calculation. These strategies are in line with a change in the Dutch guidelines (by FNT) from January 1, 2016 onward.[19] According to guidelines, a TTR of ≥70% is considered a good quality of therapy,[2] whereas a TTR < 60% is considered "unstable" in the HAS-BLED score,[18] and a TTR ≤ 45% is considered as very poor anticoagulation control.

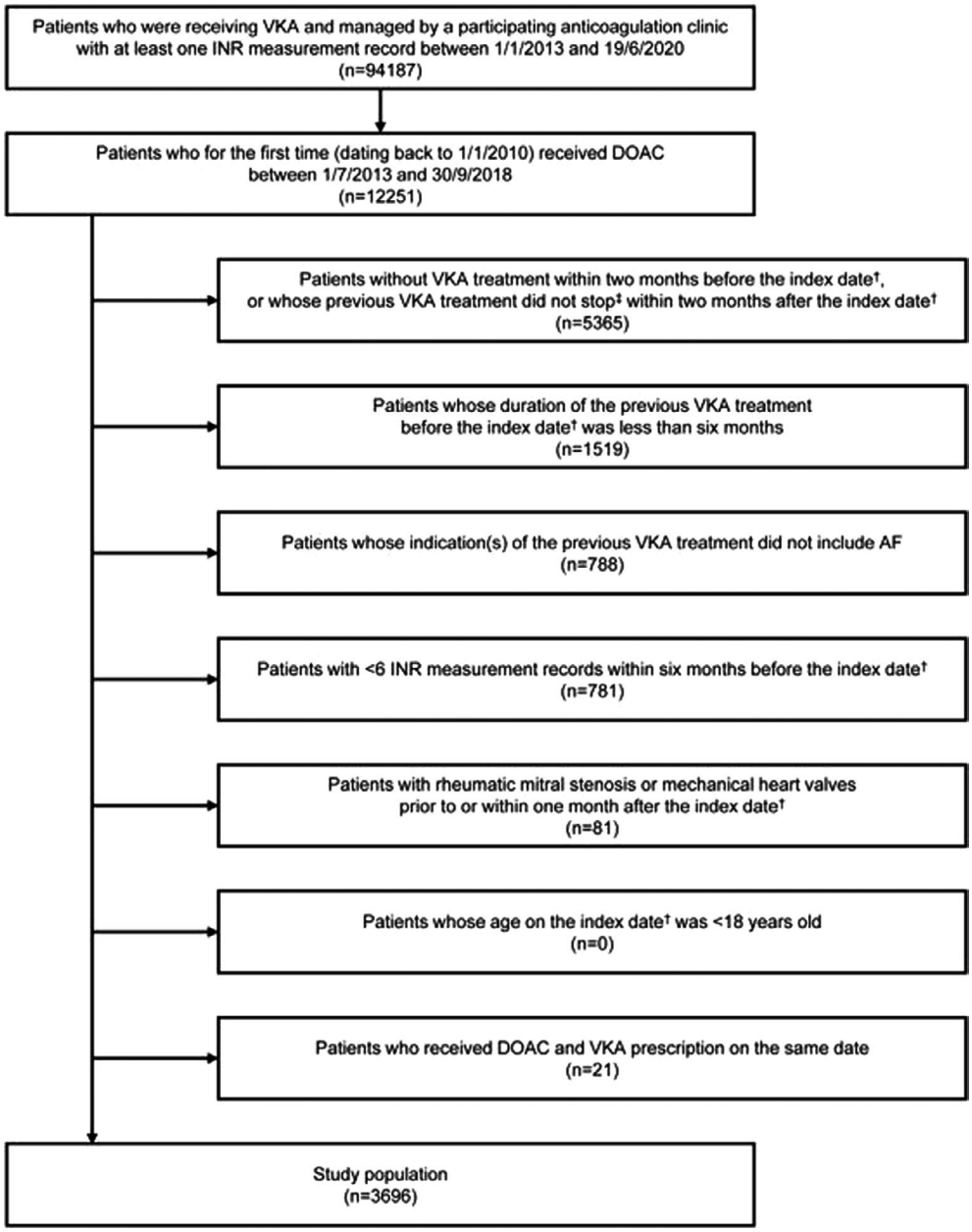

FIGURE 1 Flow chart of study population. Notes: One month was counted as 30 days. †Refer to the date of the first DOAC prescription between July 1, 2013 and September 30, 2018. ‡Determined according to the recorded end date of VKA treatment. AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio; VKA, vitamin K antagonist

2.5 | Persistence patterns

Non-persistence to DOAC was studied as the main outcome. All patients were followed from the index date until the outcome event occurred, the end of the study period (September 30, 2018) or death, whichever occurred first. As the exact amount of medication collected for each prescription was not available from the data, a conservative and previously used definition of non-persistence according to a 100-day prescription gap was employed,[14] which would also examine the prescription data between October 1, 2018 and December 31, 2018. In brief, the last available DOAC prescription before December 31, 2018 but before the first VKA prescription (if available) was examined to determine non-persistence to DOAC. Patients were considered persistent to DOAC until September 30, 2018, if the last DOAC prescription was between October 1, 2018 and December 31, 2018. If the last DOAC prescription was before October 1, 2018, a patient was considered non-persistent to DOAC from the date of the last DOAC prescription onward, unless a patient died within 100 days after the last DOAC prescription. To account for patients who discontinued their DOAC and switched back to VKA, non-persistence to OAC (either DOAC or VKA) was also studied as a separate outcome. For this outcome, if a patient discontinued DOAC but switched back to VKA, they were seen as persistent to OAC. The outcome was determined in a similar way to non-persistence to DOAC, but instead of the last

DOAC prescription, the last OAC (either DOAC or VKA) prescription was examined. In addition, we studied switching back to a VKA as another outcome. Patients who received a VKA before September 30, 2018 were considered patients switching back to a VKA, and the date of the first VKA prescription after the index date was considered the date of switching back to VKA. Death shortly after switching back to a VKA was not taken into account when determining the outcome switching back to VKA.

2.6 | Statistical analysis

Continuous variables were summarized as means ± standard deviations and categorical variables as numbers and percentages. Cumulative incidences of the study outcomes were estimated using the cumulative incidence competing risk (CICR) method, as well as plotted as cumulative incidence curves,[20] which considered all-cause mortality as a competing event. Cox regression models were employed to evaluate the associations of baseline TTR levels with the study outcomes. We used the following cut-offs to define low and high levels of TTR, namely ≤45% and >45%, ≤60% and >60%, and ≤70% and >70%. In addition to a crude model, the associations were also evaluated after adjustments for potential confounders. The following adjustment models were used: (1) adjustment for age, sex, and anticoagulation clinic; (2) adjustment for model 1 and various studied comorbidities; (3) adjustment for model 1 and baseline CHA_2DS_2-VASc score; (4) adjustment for model 1 and baseline HAS-BLED score; (5) restricted to patients with baseline CHA_2DS_2-VASc score ≥2, in addition to adjustments from model 2. To examine the robustness of calculating baseline TTR over a somewhat arbitrary period of 6 months before the switch, a sensitivity analysis was performed that calculated baseline TTR over a period of 3 months (among patients with at least 3 months of VKA use and at least three INR measurement records), after which we re-examined the cumulative incidences of the outcomes, as well as the associations between baseline TTR levels and the outcomes.

To provide more information about the study population, we performed two extra analyses with the available data we obtained. First, we explored patient profiles (including age, sex, number of persons in the household, immigration status, marital status, and standardized household income) associated with a TTR ≤ 45% by univariable logistic regression analysis. Information about the data sources of these extra information was previously described.[14] In this analysis, the patient profiles were identified 6 months before the switch, and TTR levels were determined in the same way as that in the main analysis. Second, we calculated the incidence rates of major bleeding and ischemic stroke of the study population. For major bleeding, the patients were followed from the index date until September 30, 2018, date of death, or the date when becoming non-persistent to DOACs. For ischemic stroke, only patients who became non-persistent to OACs were included and they were followed from the date when becoming non-persistent to OACs until September 30, 2018 or date of death, whichever occurred first.

All statistical analyses were performed with SPSS® Statistics (Version 25.0; IBM Corp.) and R program (R Core Team).

3 | RESULTS

3.1 | Baseline characteristics

A total of 3696 adult NVAF patients who were receiving VKA treatment and managed by a participating anticoagulation clinic and were switched to a DOAC between July 1, 2013 and September 30, 2018 were included (Figure 1). The mean age of the study population was 74.2 ± 9.5 years and 55.7% (2059/3696) were male (Table 1). The mean baseline CHA_2DS_2-VASc score was 2.5 ± 1.5, and 75.2% (2780/3696) had a baseline CHA_2DS_2-VASc score ≥ 2. The mean HAS-BLED score was 2.0 ± 1.0. The most frequently presented comorbidities in the study population were hypertension (24.3%, 897/3696), congestive heart failure (11.3%, 418/3696), diabetes mellitus (11.0%, 405/3696), and a history of myocardial infarction (8.6%, 319/3696). Patients with a baseline TTR ≤ 45% (690/3696) were on average slightly older (75.9 ± 10.1 vs. 73.9 ± 9.3 years), had a higher mean baseline CHA_2DS_2-VASc score (2.7 ± 1.5 vs. 2.5±1.5) and HAS-BLED score (2.7 ± 0.9 vs. 1.8 ± 1.0), and had higher prevalence of the comorbidities compared to patients with a baseline TTR > 45%. Information about the baseline characteristics stratified by a TTR cut-off of 60% and 70% are presented in Table 1.

3.2 | Cumulative incidence of persistence patterns

As presented in Table 2, the cumulative incidences of non-persistence to DOACs in the total study population were 5.9% (95% confidence interval [CI] 5.2%–6.7%), 7.4% (95% CI 6.6%–8.3%), 10.6% (95% CI 9.5%–11.6%), 15.1% (95% CI 13.8%–16.5%), 19.5% (95% CI 17.8%–21.2%), and 23.1% (95% CI 21.0%–25.4%) at 100 days; 6 months; 1, 2, 3, and 4 years after the index date, respectively. Stratified by baseline TTR levels, the cumulative incidence of non-persistence to DOACs in patients with a baseline TTR ≤ 45% were always higher than that in patients with a baseline TTR > 45 within the same follow-up periods (Table 2, and Figure 2). Results are similar using other cut-offs to define the levels of TTR, and for the outcome non-persistence to OACs (Table 2, and Figure S1 in supporting information). For the outcome switching back to VKAs, however, patients with a low baseline TTR appeared to have lower cumulative incidences compared to those with a high baseline TTR in the first 2 years (Table 2, and Figure S2 in supporting information).

3.3 | Associations between baseline TTR and persistence patterns

After adjusting for age, sex, anticoagulation clinic, and various comorbidities, and restricting the study population to be with a

TABLE 1 Baseline characteristics of the study population

		TTR group		TTR group		TTR group	
	Total	≤45%	>45%	≤60%	>60%	≤70%	>70%
	3696	690	3006	1430	2266	2070	1626
Age (years), mean ± SD	74.24 ± 9.49	75.86 ± 10.06	73.86 ± 9.31	75.41 ± 9.85	73.50 ± 9.18	75.08 ± 9.79	73.16 ± 8.98
Age group (years)							
18–45	NA	NA	NA	NA	NA	NA	NA
45–55	87 (2.4)	17 (2.5)	70 (2.3)	37 (2.6)	50 (2.2)	52 (2.5)	35 (2.2)
55–65	460 (12.4)	79 (11.4)	381 (12.7)	159 (11.1)	301 (13.3)	246 (11.9)	214 (13.2)
65–75	1350 (36.5)	213 (30.9)	1137 (37.8)	462 (32.3)	888 (39.2)	678 (32.8)	672 (41.3)
75–85	1333 (36.1)	252 (36.5)	1081 (36.0)	534 (37.3)	799 (35.3)	770 (37.2)	563 (34.6)
≥85	453 (12.3)	128 (18.6)	325 (10.8)	235 (16.4)	218 (9.6)	319 (15.4)	134 (8.2)
Sex							
Male	2059 (55.7)	386 (55.9)	1673 (55.7)	805 (56.3)	1254 (55.3)	1155 (55.8)	904 (55.6)
Female	1637 (44.3)	304 (44.1)	1333 (44.3)	625 (43.7)	1012 (44.7)	915 (44.2)	722 (44.4)
CHA_2DS_2-VASc score							
Mean ± SD	2.52 ± 1.47	2.74 ± 1.50	2.47 ± 1.46	2.69 ± 1.48	2.42 ± 1.46	2.65 ± 1.50	2.35 ± 1.42
0	226 (6.1)	36 (5.2)	190 (6.3)	76 (5.3)	150 (6.6)	111 (5.4)	115 (7.1)
1	690 (18.7)	101 (14.6)	589 (19.6)	223 (15.6)	467 (20.6)	351 (17.0)	339 (20.8)
≥2	2780 (75.2)	553 (80.1)	2227 (74.1)	1131 (79.1)	1649 (72.8)	1608 (77.7)	1172 (72.1)
2	1089 (29.5)	190 (27.5)	899 (29.9)	392 (27.4)	697 (30.8)	574 (27.7)	515 (31.7)
3	883 (23.9)	175 (25.4)	708 (23.6)	373 (26.1)	510 (22.5)	521 (25.2)	362 (22.3)
4	436 (11.8)	102 (14.8)	334 (11.1)	196 (13.7)	240 (10.6)	268 (12.9)	168 (10.3)
5	227 (6.1)	51 (7.4)	176 (5.9)	108 (7.6)	119 (5.3)	150 (7.2)	77 (4.7)
6	103 (2.8)	27 (3.9)	76 (2.5)	46 (3.2)	57 (2.5)	66 (3.2)	37 (2.3)
7	NA	NA	NA	14 (1.0)	23 (1.0)	26 (1.3)	11 (0.7)
8	NA	NA	NA	NA	NA	NA	NA
9	NA	NA	NA	NA	NA	NA	NA
HAS-BLED score							
Mean ± SD	1.95 ± 1.04	2.68 ± 0.93	1.79 ± 0.98	2.66 ± 0.91	1.51 ± 0.85	2.31 ± 1.04	1.50 ± 0.83
0	186 (5.0)	0 (0.0)	186 (6.2)	0 (0.0)	186 (8.2)	54 (2.6)	132 (8.1)
1	1126 (30.5)	45 (6.5)	1081 (36.0)	83 (5.8)	1043 (46.0)	373 (18.0)	753 (46.3)
2	1384 (37.4)	281 (40.7)	1103 (36.7)	615 (43.0)	769 (33.9)	821 (39.7)	563 (34.6)
≥3	1000 (27.1)	364 (52.8)	636 (21.2)	732 (51.2)	268 (11.8)	822 (39.7)	178 (10.9)
3	721 (19.5)	234 (33.9)	487 (16.2)	486 (34.0)	235 (10.4)	563 (27.2)	158 (9.7)
4	236 (6.4)	109 (15.8)	127 (4.2)	206 (14.4)	30 (1.3)	219 (10.6)	17 (1.0)
5	38 (1.0)	19 (2.8)	19 (0.6)	NA	NA	NA	NA
6	NA	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA	NA
Comorbidities							
Chronic obstructive pulmonary disease	251 (6.8)	57 (8.3)	194 (6.5)	130 (9.1)	121 (5.3)	176 (8.5)	75 (4.6)
Asthma	48 (1.3)	NA	NA	28 (2.0)	20 (0.9)	31 (1.5)	17 (1.0)
Other chronic lung diseases	47 (1.3)	10 (1.4)	37 (1.2)	24 (1.7)	23 (1.0)	33 (1.6)	14 (0.9)
Congestive heart failure	418 (11.3)	101 (14.6)	317 (10.5)	199 (13.9)	219 (9.7)	278 (13.4)	140 (8.6)
Hypertension	897 (24.3)	177 (25.7)	720 (24.0)	354 (24.8)	543 (24.0)	521 (25.2)	376 (23.1)
Myocardial infarction history	319 (8.6)	72 (10.4)	247 (8.2)	141 (9.9)	178 (7.9)	202 (9.8)	117 (7.2)

TABLE 1 (Continued)

		TTR group		TTR group		TTR group	
	Total	≤45%	>45%	≤60%	>60%	≤70%	>70%
	3696	690	3006	1430	2266	2070	1626
Abnormal liver function	46 (1.2)	13 (1.9)	33 (1.1)	25 (1.7)	21 (0.9)	34 (1.6)	12 (0.7)
Gastroesophageal reflux disease	19 (0.5)	NA	NA	NA	NA	NA	NA
Peptic ulcer disease	14 (0.4)	NA	NA	NA	NA	NA	NA
Abnormal renal function	294 (8.0)	82 (11.9)	212 (7.1)	152 (10.6)	142 (6.3)	203 (9.8)	91 (5.6)
Anemia	244 (6.6)	75 (10.9)	169 (5.6)	137 (9.6)	107 (4.7)	177 (8.6)	67 (4.1)
Coagulopathy	129 (3.5)	35 (5.1)	94 (3.1)	66 (4.6)	63 (2.8)	83 (4.0)	46 (2.8)
Diabetes mellitus	405 (11.0)	111 (16.1)	294 (9.8)	203 (14.2)	202 (8.9)	275 (13.3)	130 (8.0)
Thyroid disease	75 (2.0)	14 (2.0)	61 (2.0)	32 (2.2)	43 (1.9)	39 (1.9)	36 (2.2)
Autoimmune disease	13 (0.4)	NA	NA	NA	NA	NA	NA
Systemic connective tissue disorders	34 (0.9)	13 (1.9)	21 (0.7)	20 (1.4)	14 (0.6)	22 (1.1)	12 (0.7)
Ischemic stroke/TIA history	230 (6.2)	47 (6.8)	183 (6.1)	99 (6.9)	131 (5.8)	135 (6.5)	95 (5.8)
Alzheimer's disease	NA	NA	NA	NA	NA	NA	NA
Parkinson's disease	12 (0.3)	NA	NA	NA	NA	NA	NA
Peripheral artery disease	35 (0.9)	NA	NA	18 (1.3)	17 (0.8)	25 (1.2)	10 (0.6)
Venous thromboembolism	40 (1.1)	11 (1.6)	29 (1.0)	19 (1.3)	21 (0.9)	30 (1.4)	10 (0.6)
Deep vein thrombosis	15 (0.4)	NA	NA	NA	NA	NA	NA
Pulmonary embolism	27 (0.7)	NA	NA	13 (0.9)	14 (0.6)	NA	NA
Arterial embolism and thrombosis	24 (0.6)	NA	NA	12 (0.8)	12 (0.5)	NA	NA
Major bleeding history	257 (7.0)	59 (8.6)	198 (6.6)	122 (8.5)	135 (6.0)	174 (8.4)	83 (5.1)
Malignant tumor	286 (7.7)	60 (8.7)	226 (7.5)	132 (9.2)	154 (6.8)	188 (9.1)	98 (6.0)
Type of VKA before switch to DOAC[a]							
Acenocoumarol	2494 (67.5)	528 (76.5)	1966 (65.4)	1079 (75.5)	1415 (62.4)	1533 (74.1)	961 (59.1)
Fenprocoumon	1201 (32.5)	161 (23.3)	1040 (34.6)	350 (24.5)	851 (37.6)	536 (25.9)	665 (40.9)

Note: NA, not available as numbers were <10, which were not allowed to share according to policy of Statistics Netherlands.

Abbreviations: DOAC, direct oral anticoagulant; SD, standard deviation; TIA, transient ischemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.

[a]Other types of VKA are not presented due to a low frequency.

baseline CHA_2DS_2-VASc score ≥2, a baseline TTR ≤ 45% was associated with a higher risk of non-persistence to DOAC (Hazard ratio [HR] 1.55, 95% CI 1.22–1.97), when compared to a baseline TTR > 45% (Table 3). Similar associations were present when using other cut-offs to define the levels of TTR (for TTR ≤ 60%: HR 1.55, 95% CI 1.27–1.90; for TTR ≤ 70%: HR 1.43, 95% CI 1.16–1.76%). The direction of the association was consistent when different adjustment models were used. For the association between baseline TTR levels and non-persistence to OAC, similar results were observed (Table 3). There was no statistically significant association between baseline TTR levels and switching back to VKA (for TTR ≤ 45%: HR 0.99, 95% CI 0.65–1.53; TTR ≤ 60%: HR 1.14, 95% CI 0.82–1.58; for TTR ≤ 70%: HR 1.02, 95% CI 0.74–1.41).

3.4 | Sensitivity analysis

The sensitivity analysis included 4100 patients in the study population, for which the baseline TTR was calculated over a period of 3 months, with a mean age of 73.9 years, and a male sex proportion of 56.6% (2319/4100). The cumulative incidences of the study outcomes were robust after changing the period of INR measurement records used for the calculation of baseline TTR (Table S2, Figures S3-S5 in supporting information). Consistently, the associations between baseline TTR levels and non-persistence to DOACs were similar, as a baseline TTR ≤ 45% was associated with a higher risk of non-persistence to DOACs (hazard ratio [HR] 1.41, 95% CI 1.15–1.73). Results using other cutoffs for baseline TTR levels

TABLE 2 Cumulative incidences of the study outcomes[a]

	Non-persistence to DOAC				Non-persistence to OAC (DOAC or VKA)				Switching back to VKA			
	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)
Total												
0–100 days	911.46	3696	213	5.92 (5.18–6.72)	937.86	3696	80	2.25 (1.81–2.78)	936.69	3696	102	2.93 (2.41–3.52)
0–6 months	1570.76	3696	260	7.39 (6.55–8.28)	1626.66	3696	118	3.41 (2.84–4.05)	1617.45	3696	130	3.73 (3.14–4.40)
0–1 year	2798.66	3696	350	10.55 (9.53–11.64)	2923.37	3696	188	5.87 (5.09–6.73)	2894.69	3696	163	4.88 (4.18–5.65)
0–2 years	4458.23	3696	446	15.14 (13.82–16.51)	4706.51	3696	282	10.31 (9.17–11.53)	4641.61	3696	187	5.99 (5.18–6.88)
0–3 years	5356.69	3696	497	19.47 (17.76–21.23)	5694.06	3696	335	14.63 (13.07–16.28)	5595.52	3696	195	6.66 (5.74–7.67)
0–4 years	5803.17	3696	521	23.14 (20.96–25.39)	6197.42	3696	360	18.38 (16.29–20.57)	6078.26	3696	203	8.25 (6.87–9.79)
TTR ≤ 45%												
0–100 days	165.85	690	42	6.28 (4.61–8.29)	169.19	690	26	4.05 (2.74–5.75)	171.78	690	13	2.12 (1.21–3.44)
0–6 months	281.82	690	55	8.47 (6.48–10.78)	288.57	690	36	5.58 (3.99–7.55)	293.23	690	19	2.96 (1.85–4.50)
0–1 year	487.47	690	83	14.03 (11.33–17.01)	502.40	690	59	10.18 (7.86–12.85)	511.19	690	24	3.93 (2.58–5.70)
0–2 years	743.68	690	110	21.39 (17.76–25.26)	775.49	690	84	16.91 (13.61–20.53)	786.87	690	30	5.60 (3.80–7.87)
0–3 years	833.88	690	119	27.85 (22.56–33.38)	876.82	690	92	22.41 (17.64–27.55)	885.39	690	33	7.69 (4.88–11.30)
0–4 years	870.72	690	121	30.63 (24.33–37.15)	918.57	690	96	28.08 (21.16–35.39)	926.48	690	35	11.61 (6.32–18.66)
TTR > 45%												
0–100 days	745.60	3006	171	5.84 (5.03–6.73)	768.66	3006	54	1.84 (1.40–2.38)	764.91	3006	89	3.11 (2.52–3.79)
0–6 months	1288.94	3006	205	7.14 (6.23–8.12)	1338.09	3006	82	2.92 (2.34–3.59)	1324.22	3006	111	3.91 (3.24–4.67)
0–1 year	2311.20	3006	267	9.79 (8.70–10.95)	2420.97	3006	129	4.92 (4.13–5.80)	2383.5	3006	139	5.09 (4.30–5.96)
0–2 years	3714.56	3006	336	13.79 (12.41–15.26)	3931.02	3006	198	8.89 (7.72–10.16)	3854.74	3006	157	6.09 (5.20–7.08)
0–3 years	4522.82	3006	378	17.88 (16.10–19.74)	4817.24	3006	243	13.10 (11.47–14.84)	4710.13	3006	162	6.56 (5.59–7.63)
0–4 years	4932.44	3006	400	21.72 (19.40–24.14)	5278.86	3006	264	16.68 (14.50–19.00)	5151.79	3006	168	7.91 (6.51–9.49)
TTR ≤ 60%												
0–100 days	344.48	1430	80	5.77 (4.63–7.09)	353.42	1430	38	2.83 (2.05–3.81)	354.54	1430	38	2.87 (2.08–3.86)
0–6 months	586.01	1430	108	8.12 (6.72–9.67)	604.15	1430	62	4.76 (3.69–6.02)	604.86	1430	45	3.37 (2.49–4.44)
0–1 year	1019.66	1430	157	12.84 (11.01–14.81)	1059.94	1430	101	8.52 (7.00–10.22)	1062.15	1430	57	4.50 (3.45–5.75)
0–2 years	1553.52	1430	208	19.88 (17.37–22.51)	1633.18	1430	149	15.00 (12.75–17.42)	1634.75	1430	68	5.99 (4.66–7.55)
0–3 years	1775.08	1430	229	26.28 (22.77–29.92)	1882.15	1430	172	21.58 (18.28–25.06)	1877.01	1430	73	7.42 (5.65–9.49)
0–4 years	1876.42	1430	234	29.14 (24.95–33.45)	1998.22	1430	178	25.15 (20.90–29.61)	1989.54	1430	77	10.57 (7.28–14.56)
TTR > 60%												

TABLE 2 (Continued)

	Non-persistence to DOAC				Non-persistence to OAC (DOAC or VKA)				Switching back to VKA			
	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)	Follow-up (years)	No. at risk	No. event	Cumulative incidence (95% CI) (%)
0–100 days	566.97	2266	133	6.01 (5.07–7.05)	584.44	2266	42	1.90 (1.39–2.53)	582.16	2266	64	2.97 (2.32–3.74)
0–6 months	984.75	2266	152	6.95 (5.93–8.07)	1022.51	2266	56	2.59 (1.98–3.33)	1012.59	2266	85	3.95 (3.19–4.84)
0–1 year	1779.00	2266	193	9.22 (8.02–10.51)	1863.43	2266	87	4.3 (3.47–5.25)	1832.54	2266	106	5.11 (4.21–6.12)
0–2 years	2904.71	2266	238	12.52 (11.03–14.10)	3073.33	2266	133	7.67 (6.44–9.03)	3006.86	2266	119	6.03 (5.02–7.16)
0–3 years	3581.62	2266	268	16.12 (14.22–18.12)	3811.91	2266	163	11.17 (9.49–13)	3718.50	2266	122	6.39 (5.31–7.59)
0–4 years	3926.75	2266	287	20.17 (17.63–22.83)	4199.20	2266	182	15.07 (12.72–17.61)	4088.73	2266	126	7.49 (6.03–9.15)
TTR ≤ 70%												
0–100 days	500.92	2070	122	6.08 (5.09–7.18)	515.00	2070	56	2.86 (2.19–3.66)	515.89	2070	59	3.04 (2.35–3.87)
0–6 months	855.76	2070	156	8.03 (6.87–9.29)	884.34	2070	85	4.46 (3.60–5.46)	883.78	2070	68	3.50 (2.75–4.39)
0–1 year	1498.74	2070	214	11.83 (10.38–13.39)	1560.77	2070	133	7.61 (6.41–8.93)	1559.24	2070	82	4.41 (3.54–5.42)
0–2 years	2308.08	2070	278	17.82 (15.85–19.88)	2428.50	2070	194	13.22 (11.46–15.10)	2423.78	2070	95	5.59 (4.53–6.80)
0–3 years	2678.31	2070	307	23.32 (20.66–26.09)	2840.82	2070	225	18.77 (16.28–21.40)	2826.15	2070	100	6.49 (5.20–7.96)
0–4 years	2853.71	2070	315	26.23 (22.97–29.59)	3041.46	2070	233	21.74 (18.57–25.09)	3019.35	2070	106	9.37 (6.90–12.28)
TTR > 70%												
0–100 days	410.54	1626	91	5.71 (4.64–6.93)	422.85	1626	24	1.50 (0.99–2.19)	420.81	1626	43	2.79 (2.06–3.69)
0–6 months	715.00	1626	104	6.60 (5.45–7.90)	742.32	1626	33	2.12 (1.49–2.93)	733.67	1626	62	4.01 (3.11–5.07)
0–1 year	1299.92	1626	136	9.03 (7.64–10.56)	1362.60	1626	55	3.79 (2.89–4.86)	1335.46	1626	81	5.43 (4.35–6.67)
0–2 years	2150.15	1626	168	12.19 (10.48–14.03)	2278.01	1626	88	7.04 (5.67–8.59)	2217.83	1626	92	6.48 (5.26–7.86)
0–3 years	2678.38	1626	190	15.65 (13.50–17.95)	2853.24	1626	110	10.42 (8.54–12.51)	2769.37	1626	95	6.95 (5.64–8.43)
0–4 years	2949.45	1626	206	20.00 (17.09–23.09)	3155.96	1626	127	14.90 (12.18–17.88)	3058.91	1626	97	7.65 (6.07–9.46)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; TTR, time in therapeutic range; VKA, Vitamin K antagonist.

[a]Estimated by the cumulative incidence competing risk (CICR) method.

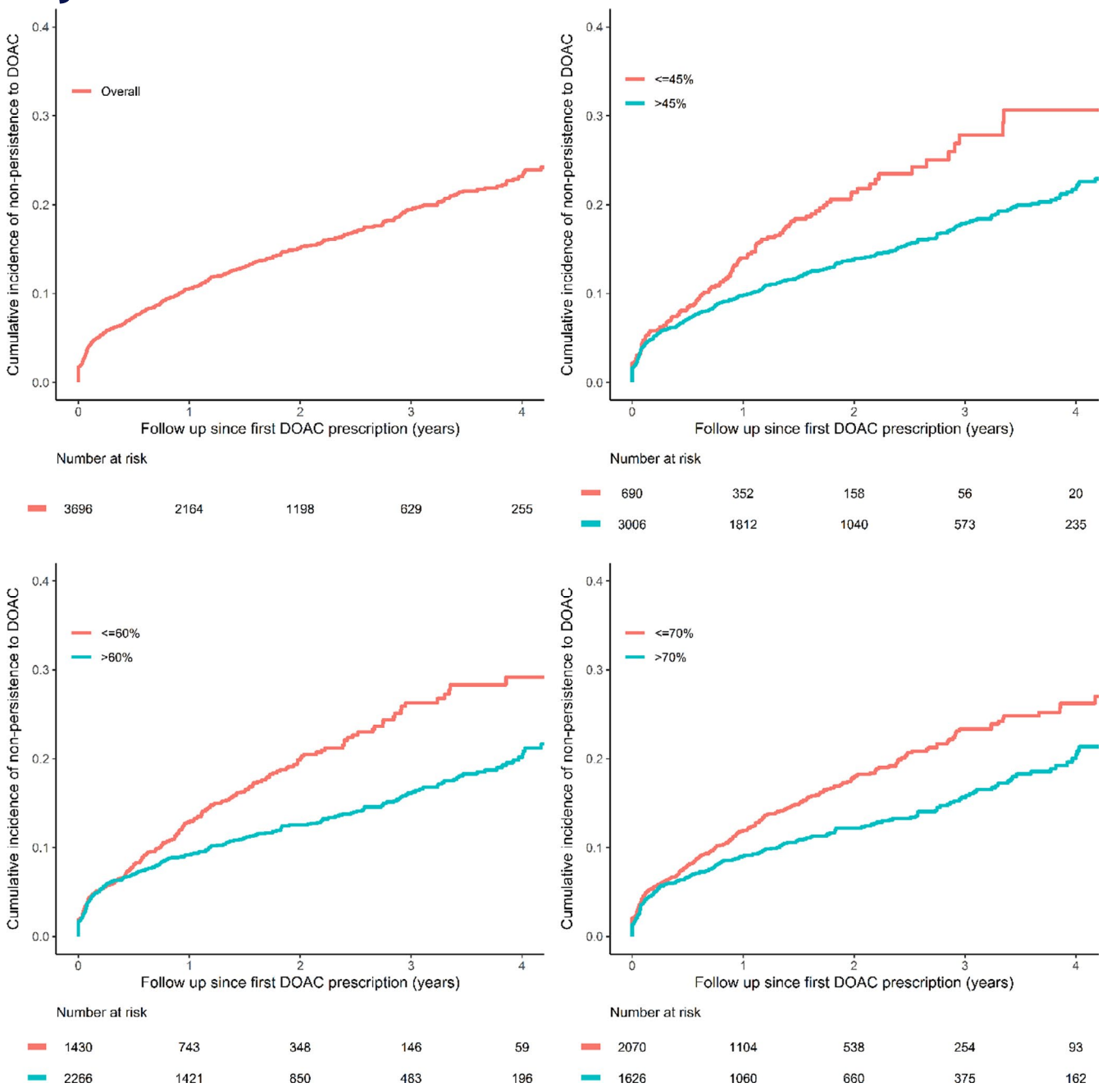

FIGURE 2 Cumulative incidence of non-persistence to DOAC by baseline TTR levels. Note: Estimated by the cumulative incidence competing risk (CICR) method. DOAC, direct oral anticoagulant; TTR, time in therapeutic range

and other study outcomes are presented in Table S3 in supporting information.

3.5 | Extra analyses

As presented in Table S4 in supporting information, among the investigated patient profiles identified in 6 months before the switch, an increase in age, living alone in a household, the first generation of immigrants (compared to the native Dutch), not married, and a low standardized household income were associated with an increased risk of a TTR ≤ 45%. When the patients were followed from the switch until becoming non-persistent to DOACs, the incidence rate of major bleeding was 1.55 (95% CI 1.25–1.91) per 100 person-years. For patients with a baseline TTR ≤ 45%, the incidence rate was 1.84 (95% CI 1.05–2.99) per 100 person-years, which appeared to be higher compared to those with a baseline TTR > 45% (1.50, 95% CI 1.18–1.88, per 100 person-years). For patients who became non-persistent to OACs, the incidence rate of ischemic stroke was 2.97 (95% CI 1.28–5.86) per 100 person-years after becoming non-persistent to OACs.

TABLE 3 Associations between baseline TTR levels and the study outcomes

	Observation time (PYs)	No. Event	Incidence rate (95% CI) (per 100 PYs)	HR (95% CI)					
				Crude	Model 1	Model 2	Model 3	Model 4	Model 5
Non-persistence to DOAC									
TTR > 45%	5061.89	412	8.14 (7.37–8.96)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 45%	881.68	122	13.84 (11.49–16.52)	1.57 (1.28–1.92)	1.62 (1.32–1.99)	1.62 (1.32–1.99)	1.61 (1.31–1.98)	1.64 (1.31–2.04)	1.55 (1.22–1.97)
TTR > 60%	4035.40	299	7.41 (6.59–8.30)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 60%	1908.16	235	12.32 (10.79–13.99)	1.53 (1.29–1.82)	1.58 (1.33–1.88)	1.57 (1.32–1.87)	1.57 (1.31–1.86)	1.77 (1.43–2.19)	1.55 (1.27–1.90)
TTR > 70%	3040.64	216	7.10 (6.19–8.12)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 70%	2902.92	318	10.95 (9.78–12.23)	1.42 (1.20–1.70)	1.48 (1.24–1.76)	1.48 (1.24–1.77)	1.46 (1.22–1.75)	1.50 (1.24–1.81)	1.43 (1.16–1.76)
Non-persistence to OAC									
TTR > 45%	5422.74	279	5.15 (4.56–5.79)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 45%	930.64	97	10.42 (8.45–12.72)	2.02 (1.60–2.55)	2.06 (1.62–2.61)	2.02 (1.59–2.57)	2.02 (1.60–2.56)	2.02 (1.57–2.61)	1.97 (1.49–2.60)
TTR > 60%	4320.82	197	4.56 (3.94–5.24)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 60%	2032.56	179	8.81 (7.56–10.20)	1.92 (1.57–2.36)	1.96 (1.59–2.41)	1.93 (1.57–2.38)	1.94 (1.58–2.38)	2.19 (1.70–2.83)	1.95 (1.52–2.49)
TTR > 70%	3257.40	139	4.27 (3.59–5.04)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 70%	3095.99	237	7.66 (6.71–8.69)	1.79 (1.45–2.21)	1.83 (1.48–2.27)	1.80 (1.45–2.24)	1.81 (1.46–2.25)	1.81 (1.44–2.28)	1.79 (1.38–2.32)
Switching back to VKA									
TTR > 45%	5291.62	168	3.17 (2.71–3.69)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 45%	937.45	35	3.73 (2.60–5.19)	1.01 (0.70–1.45)	1.09 (0.75–1.57)	1.11 (0.76–1.61)	1.09 (0.75–1.57)	1.10 (0.75–1.63)	0.99 (0.65–1.53)
TTR > 60%	4206.51	126	3.00 (2.50–3.57)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 60%	2022.57	77	3.81 (3.00–4.76)	1.09 (0.82–1.45)	1.17 (0.88–1.56)	1.17 (0.88–1.57)	1.16 (0.87–1.55)	1.26 (0.89–1.78)	1.14 (0.82–1.58)
TTR > 70%	3156.69	97	3.07 (2.49–3.75)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
TTR ≤ 70%	3072.39	106	3.45 (2.82–4.17)	0.97 (0.74–1.28)	1.04 (0.79–1.38)	1.06 (0.80–1.41)	1.04 (0.78–1.37)	1.06 (0.78–1.44)	1.02 (0.74–1.41)

Note: The following adjustment models were used: (a) model 1, adjustment for age, sex, and anticoagulation clinic; (b) model 2, adjustment for model 1 and various studied comorbidities, including chronic obstructive pulmonary disease, asthma, other chronic lung diseases, congestive heart failure, hypertension, myocardial infarction history, abnormal liver function, gastroesophageal reflux disease, peptic ulcer disease, abnormal renal function, anemia, coagulopathy, diabetes mellitus, thyroid disease, autoimmune disease, systemic connective tissue disorder, ischemic stroke/transient ischemic attack, Alzheimer's disease, Parkinson's disease, peripheral artery disease, deep vein thrombosis, pulmonary embolism, arterial embolism and thrombosis, major bleeding history, and malignant tumor; (c) model 3, adjustment for model 1 and baseline CHA_2DS_2-VASc score; (d) model 4, adjustment for model 1 and baseline HAS-BLED score; (e) model 5, restricted to patients with baseline CHA_2DS_2-VASc score ≥2, in addition to adjustments from model 2.

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; OAC, oral anticoagulant; PY, person-year; TTR, time in therapeutic range; VKA, vitamin K antagonist.

4 | DISCUSSION

In this cohort study, adult NVAF patients who switched from a VKA to a DOAC between 2013 and 2018 were followed. Persistence to DOACs in the study population was assessed and related to baseline TTR levels at the moment of switching from a VKA to a DOAC. The main finding was that persistence to DOACs was worse for patients with a lower baseline TTR than for patients with a higher baseline TTR, which was consistent over all used cut-off points to define a low level of baseline TTR.

So far there are few studies that investigate DOAC persistence after switching from a VKA due to a low TTR, even though this is common practice and is advised by guidelines.[2] Our results are consistent with another cohort study ($n = 8016$, reported as conference abstract) with data from the Veterans Health Administration, which demonstrated that former VKA patients who were switched to a DOAC with a low pre-switch TTR (<50%) were less likely to achieve good DOAC adherence (as identified by the proportion of days covered [PDC] ≥ 80% after 1 year) compared to patients with a higher pre-switch TTR (PDC ≥ 80% was 70% [2277/4532] in low TTR group vs. 82% [1989/3484] in the high TTR group).[21] However, because this study was so far only published as an abstract, many details about the study (e.g., how the authors handled potential confounding factors) are unknown. In this study treatment adherence was studied, as opposed to treatment persistence (with long follow-up periods) in our study, which contributes to the novelty of our current study. Also, the Netherlands has a very well-developed system of VKA monitoring (e.g. thrombosis services), which makes it likely that the low TTR patients identified in our study were really patients with a low TTR. This could be different for other countries.

Persistence patterns to DOACs among NVAF patients have been studied earlier and show large variation between studies, which may be related to the use of different definitions for non-persistence.[11-13] In a recent meta-analysis that included 48 observational studies, the pooled proportion of persistence to DOAC after 1 year was 62% (95% CI 56%–68%).[15] In a previous nationwide cohort study from the Netherlands in which we studied non-persistence (according to the same definition as we used in this study) among NVAF patients and its association with clinical outcomes, the proportion of persistence to DOACs was 82.6% (95% CI 82.4–82.9%) at 1 year and 66.5% (95% CI 66.0–67.0%) at 4 years of follow-up.[14] The present study found a slightly higher proportion of persistence to DOACs compared to previous studies. This better persistence may be explained either by the use of a conservative definition compared to other studies,[15] or by differences in studied populations compared to our previous study.[14]

Suboptimal persistence to DOAC is only relevant if this also impacts prognosis in terms of clinical outcomes. Intuitively, this should be the case as "drugs don't work in patients who don't take them" (C. Everett Knoop, MD, 1985). Indeed, we have previously shown that non-persistence to OACs is associated with an increased risk of ischemic stroke (HR 1.58, 95% CI 1.29–1.93).[14] In another large cohort study, a similar association was observed.[22] Due to the limited sample size, we did not investigate the association between non-persistence to OACs and clinical outcomes in the current study. However, it could be observed that the incidence rate of ischemic stroke for patients who became non-persistent to OACs in our study was rather high (2.97, per 100 person-years), especially compared to the incidence rate we reported in our previous study among the newly diagnosed NVAF patients in the Netherlands who were persistent to OAC (0.94 per 100 person-years).[14] These results suggest that non-persistence to DOACs is a relevant issue in terms of prognosis.

Even though guidelines suggest VKA patients with TTR < 70% should be considered for switching to DOAC therapy,[2] the findings of the present study (i.e., patients with a lower baseline TTR have a higher risk of becoming non-persistent to DOAC) suggest a careful consideration on whether this strategy is indeed most optimal for every patient. A low TTR can be caused by several factors,[23] including low therapy adherence or persistence during VKA treatment.[24,25] In some situations, low TTR can be seen as a proxy for low therapy adherence or persistence to VKA.[26] Switching a patient with low TTR from a VKA to a DOAC will likely just shift the problem from low persistence to VKAs to low persistence to DOACs. Because DOACs do not require regular monitoring in contrast to VKA, and many DOAC patients are not regularly seen by their treating physician for evaluation of their anticoagulant use,[27] the problem of non-persistence to DOACs may go unnoticed. Therefore, more emphasis on other options for improvement of TTR (such as patient education, more frequent INR monitoring[2]) or better guidance while using DOACs should be considered.[26] The extra analyses we performed in the study reveal several potential risk factors of a low TTR when receiving VKA treatment, which may provide insights into the improvement of TTR.

Our study has several strengths. First, the study provided a relatively large sample size and included all eligible patients from three different anticoagulation clinics. Second, when evaluating the association between a low baseline TTR level and risk of DOAC non-persistence, many potential confounding variables (age, sex, anticoagulation clinic, various comorbidities, the CHA_2DS_2-VASc score, and the HAS-BLED score) were accounted for in our analyses. In addition, by using a conservative definition of non-persistence (using a 100-day gap, which was necessary due to the absence of data on the amount of medication for each prescription),[14] the reported cumulative incidences of non-persistence will at most underestimate the true non-persistence rate, limiting the chance of a statistical type I error. Also, the sensitivity analysis showed that the associations were robust when changing the period of INR measurement records used for TTR calculation.

4.1 | Limitations

There are also some limitations of the study. First, the exact amount of DOAC medication for each prescription was unknown. For this reason, calculation of the PDC (commonly used in pharmacoepidemiologic studies to quantify medication adherence) was

not possible. We circumvented this issue by using a conservative definition of DOAC non-persistence which is also an often-used outcome in drug therapy studies.[28] Second, specific DOAC types were unknown and therefore we cannot comment on whether non-persistence was different between different DOAC types. Third, because the reasons patients had a low TTR or were non-persistent to DOACs were unknown, we were unable to take this into account in our analysis. The extra analyses we performed in the study may provide some information about this. For example, in our study the patients with a baseline TTR ≤ 45% showed higher incidence rate of major bleeding than those with a baseline TTR > 45%, suggesting major bleeding could be one of the reasons for non-persistence to DOACs, which may help to better understand how to optimize DOAC treatment adherence. Due to lack of data residual (unmeasured) confounding cannot be completely ruled out. Last, due to our criterion in which we only selected patients into the study population with at least six INR measurement records within 6 months before switching to DOAC, we may have not included those who were allowed to not visit the anticoagulation clinic for a longer period.

5 | CONCLUSIONS

NVAF patients who switched to DOACs from VKAs due to a low TTR were at higher risk of being non-persistent to DOACs compared to those switchers with a high TTR. Our results suggest that considerations about switching patients with a low TTR on VKA therapy to DOACs must be made carefully and that for some patients more extensive guidance while using DOACs could be beneficial.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

M. M. A. Toorop, Q. Chen, and W. M. Lijfering designed the research. F. J. M. van der Meer, M. C. Nierman, L. Goede, L. Faber, and M. J. H. A. Kruip collected the data. M. M. A. Toorop and Q. Chen analyzed the data. M. M. A. Toorop and Q. Chen wrote the manuscript. Q. Chen, M. J. H. A. Kruip, F. J. M. van der Meer, M. C. Nierman, L. Goede, L. Faber, S. C. Cannegieter, and W. M. Lijfering revised the manuscript for important intellectual content.

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SUPPORTING INFORMATION

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