Patterns of long-term use of non-vitamin K antagonist oral anticoagulants for non-valvular atrial fibrillation: Quebec observational study

Running title: NOACs: Persistence of use in Quebec

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Key words

treatment persistence, drug utilization, pharmacoepidemiology

Key points

- Real-life data on long-term drug utilization of NOACs in non-valvular atrial fibrillation are still scarce.
- Our population-based cohort study showed that patients of advanced age with high thromboembolic risk were less likely to initiate treatment with NOACs than with VKAs.
- One out of four patients initiating VKAs switched from VKAs to NOACs during the study period.
- NOAC users showed a higher treatment persistence than VKA users in the first 3 years.
- Patients of advanced age with high thromboembolic risk were less likely to discontinue treatment with oral anticoagulants.

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ABSTRACT

Purpose

Studies on long-term utilization of non-vitamin K antagonist oral anticoagulants (NOACs) in non-valvular atrial fibrillation (NVAF) are scarce. We evaluated predictors of use and long-term persistence of NOACs in a real-world setting.

Methods

This population-based cohort study used the computerized databases of the Canadian Province of Quebec's health insurance. Patients with a first NVAF diagnosis from 2011 until 2014 were included. A logistic regression model yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of treatment initiation with NOACs versus VKAs. Cox proportional hazards models yielded adjusted hazard ratios (HRs) and 95% CIs for predictors of switching from VKAs to NOACs versus remaining on VKAs, and for predictors of discontinuation of anticoagulation treatment.

Results

Of the 62,867 newly diagnosed NVAF patients, 14,646 initiated NOACs and 17,685 VKAs. Initiation with NOACs was less likely for patients ≥ 80 years old (OR 0.55, 95% CI 0.41-0.73) or with CHA_2DS_2-VASc ≥ 2 (OR 0.49, 95% CI 0.42-0.57). Switching from VKAs to NOACs was less likely for patients with chronic kidney disease (HR 0.53, 95% CI 0.48-0.59). After 3 years, persistence was 54% with NOACs and 25% with VKAs. Discontinuation of anticoagulation treatment was less likely for patients ≥ 80 years old (HR 0.47, 95% CI 0.40-0.55) or with

CHA_2DS_2-VASc ≥ 2 (HR 0.64, 95% CI 0.57-0.70).

Conclusions

Older, high-risk patients are less likely to initiate NOACs than VKAs. NOAC users show a higher long-term persistence than VKA users, and older, high-risk patients are less likely to discontinue anticoagulation treatment.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia currently affecting about 2.3 million people in the United States.[1] It increases 5-fold the risk of stroke and 2-fold the risk of mortality,[2] and the 30-day case-fatality in patients with AF is approximately 10%.[3] In preventing stroke and stroke associated mortality in AF, vitamin K antagonists (VKAs) have long been the gold standard. However, VKAs are prone to drug-drug interactions and depict a narrow therapeutic window, which necessitates monitoring to keep patients within a specific range of International Normalized Ratio (INR).[4] Moreover, the observed treatment persistence, i.e., the duration of time between drug initiation and drug discontinuation, is low, since up to 40% of VKA patients discontinue their therapy during the first 12 months.[5]

The non-vitamin antagonist oral anticoagulants (NOACs) showed similar or improved efficacy and safety compared to VKAs in randomized controlled trials in patients with non-valvular atrial fibrillation (NVAF),[6] and are simpler to use since they do not require INR monitoring. However, more data on real-life utilization of NOACs are needed. Areas of uncertainty include treatment initiation in incident NVAF patients, particularly regarding factors associated with the choice of specific oral anticoagulants.[7-11] Moreover, reasons for switching from VKAs to NOACs remain largely elusive.[12,13] In addition, although several studies comparing treatment persistence among NOAC and VKA users have detected higher rates in the former group, the majority of them had a limited follow-up.[5,14].

Thus, the objective of this study was to evaluate treatment initiation, switching, and persistence in patients with NVAF under oral anticoagulation based on a population-based cohort with long-term follow-up.

METHODS

Data source

This study used the computerized databases of the Canadian Province of Quebec's health insurance (RAMQ), which is responsible for administering universal healthcare services for the province of Québec, Canada. The RAMQ contains information on demographics, medical services, hospital discharges, and filled outpatient drug prescriptions. It has been extensively used for research purposes in the past,[15-21] including studies on oral anticoagulation in patients with NVAF.[22] The accuracy of linkage between the single RAMQ databases has been shown to be high.[15,23] A detailed description of their structure can be found elsewhere.[22]

Study population

From the source population of all individuals in the RAMQ, we identified all patients ≥ 40 years of age, with a first inpatient or outpatient diagnosis of AF between January 1, 2006 and December 31, 2014. This time period spanned both the periods before and after the introduction of dabigatran as the first NOAC for the treatment of NVAF in Quebec, i.e., January 2011. Cohort entry was defined as the date of the first inpatient or outpatient AF diagnosis. If the diagnosis occurred during hospitalization, cohort entry was defined as the date of hospital discharge. All cohort members were required to have RAMQ medication coverage for at least 1 year prior to cohort entry to provide sufficient baseline information on comorbidities and prior medication use. To confirm the incident nature of the NVAF diagnosis, we excluded all patients with any mention of AF prior to cohort entry or with a history of mitral stenosis, valvular repair, prosthetic heart valve, or hyperthyroidism. Moreover, in order to consider only incident users of oral

anticoagulants, we further excluded patients with a prescription of any oral anticoagulant in the last year before cohort entry. All cohort members were followed until the patient's date of emigration, leaving the prescription drug program, death or end of study period, i.e. December 31, 2014. All outpatient prescriptions for NOACs approved for NVAF in Quebec during the study period (i.e., dabigatran, rivaroxaban, apixaban) and for VKAs, which were dispensed during follow-up were identified. For each prescription, the dispensing date along with product name, drug formulation, dose and duration were obtained.

Study outcomes

The study outcomes were the following: (i) initiation of anticoagulant treatment with NOACs relative to VKAs, (ii) treatment switch from VKAs to NOACs, and (iii) treatment persistence. Persistence of use for NOACs or VKAs was quantified for each patient as the time to treatment discontinuation. Thus, the first treatment received after cohort entry was identified and every subsequent prescription of this treatment with its duration was applied to calculate the continuous use of the initiating treatment.

Exposure definition

Patients were considered continuously exposed (persistent) to VKAs or NOACs if the duration of 1 prescription overlapped with the date of the subsequent prescription. In the event of non-overlap, we allowed for a 30-day grace period between 2 successive prescriptions to account for delays in refilling and variations in patient drug adherence. Overlaps in prescription times were not cumulated. Treatment switches were considered as treatment discontinuation except for

switches within the same group of oral anticoagulants (e.g., from 1 NOAC to another NOAC).

Covariates

Covariates measured at cohort entry included age, sex, calendar year of NVAF diagnosis, time from NVAF diagnosis to anticoagulant treatment initiation, and in-hospital NVAF diagnosis. Baseline comorbidities were measured in the year prior to cohort entry and included cardiovascular comorbidities (arterial hypertension, myocardial infarction, diabetes mellitus, venous thromboembolism, congestive heart failure, ischemic stroke, vascular disease), prior bleeding events (intracranial hemorrhage, gastrointestinal bleeding, other bleedings), blood dyscrasias, predisposition to falls, dementia or schizophrenia, liver disease, chronic kidney disease, and cancer. The CHA_2DS_2-VASc score (**c**ongestive heart failure, arterial **h**ypertension, **a**ge ≥ 75 [doubled], **d**iabetes mellitus, **s**troke [doubled], **v**ascular disease, **a**ge 65-74, **s**ex **c**ategory: female sex) was computed for the year period prior to cohort entry to assess thromboembolic risk.[24] Moreover, the use of antiplatelet agents between cohort entry and anticoagulant treatment initiation was assessed.

Data analysis

To identify predictors of treatment initiation with NOACs relative to VKAs after NVAF diagnosis, a logistic regression model was used. For each predictor crude and adjusted odds ratios (ORs) of NOAC treatment initiation were estimated along with their 95% confidence intervals (CIs). This analysis was restricted to the cohort of patients diagnosed after January 2011 who had the possibility to initiate either drug. The cohort of patients diagnosed with NVAF prior to January

2011 was used to provide a baseline measure of VKA initiators in the absence of NOACs.

To identify predictors of switching to NOACs relative to remaining on VKAs, a Cox proportional hazards model was used. For each predictor crude and adjusted hazard ratios (HRs) of switching from initial VKA treatment to a NOAC were estimated along with their 95% CIs. The analysis was conducted in the cohort initiating VKAs in or after January 2011, from the first VKA prescription to the minimum date among switch to NOACs, end of study, end of insurance, or death.

To identify predictors of treatment discontinuation (end or persistence) in users of oral anticoagulants, a Cox proportional hazards model was used. For each predictor crude and adjusted HRs of anticoagulant treatment discontinuation were estimated along with the corresponding 95% CIs. Moreover, Kaplan-Meier curves were used to plot the probability of persistence with NOACs or VKAs for the first 3 years of treatment. The analysis of treatment persistence was based on the cohort of patients diagnosed with NVAF in or after January 2011 who had initiated VKAs or NOACs. The cohort of patients diagnosed with NVAF prior to January 2011 was used to provide a baseline measure of VKA persistence in the absence of NOACs.

Sensitivity analyses

We conducted 2 sensitivity analyses to test the robustness of our results on treatment persistence. First, we used difference grace periods (60 days or 50% of the duration of the last prescription) to define continuous drug exposure (persistence) in case of non-overlapping prescriptions.[22] Second, the probability of treatment persistence for the first 3 years of treatment was replotted using Kaplan-Meier curves after defining switchers from VKAs to NOACs and vice

versa as continuous users of the initial treatment, in order to assess persistence of overall oral anticoagulation. All statistical procedures were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC). Database access was approved by the Commission d'accès à l'information and the study protocol by the Ethics Committee of the Jewish General Hospital, Montreal, QC, Canada.

RESULTS

The source population included 323,289 subjects with at least 1 diagnosis code of AF during the period 2006-2014, with a total of 138,616 patients satisfying study cohort criteria **(Figure 1**). Of those, 62,867 were diagnosed with NVAF in or after January 2011, when NOACs became available, with 32,431 (52%) initiating oral anticoagulant treatment between 2011 and 2014.

Table 1 displays the baseline characteristics of patients diagnosed with NVAF in or after January 2011 according to treatment initiation with NOACs (n = 14,746) or VKAs (n = 17,685), along with the crude and adjusted ORs of treatment initiation with NOACs relative to VKAs. Most patients started treatment within 90 days of NVAF diagnosis (84% for NOAC users, 91% for VKA users). Age ≥ 80 years, prior myocardial infarction, prior venous thromboembolism, congestive heart failure, vascular disease, blood dyscrasias, chronic kidney disease, liver disease, and a CHA_2DS-VASc score ≥ 2 were associated with the lowest probability of NOAC initiation. In contrast, NVAF diagnosis after 2011 and delayed treatment initiation with oral anticoagulants following NVAF diagnosis (>30 days) were associated with the highest probability of NOAC initiation.

Among the 17,685 patients diagnosed with NVAF in or after January 2011 initiating VKAs, 4763 (27%) switched from VKAs to NOACs during follow-up (**Table 2**). The treatment switch analysis showed that prior myocardial infarction, prior venous thromboembolism, and chronic kidney disease were associated with the lowest probability of switching from VKAs to NOACs as compared to remain on VKAs. In contrast, age 50-69 years, NVAF diagnosis after 2011, and liver disease were associated with the highest probability of switching from VKAs to NOACs as compared to remain on VKAs. Among the 14,746 patients diagnosed with NVAF in or after

January 2011 initiating NOACs, 789 (5%) switched to VKAs during follow-up.

The treatment discontinuation analysis showed that initiation of NOACs, age ≥ 50 years, and a CHA_2DS_2-VASc score ≥ 2 were associated with the lowest risk of discontinuation of oral anticoagulation (**Table 3**). In contrast, delayed treatment initiation following NVAF diagnosis (>180 days), prior myocardial infarction, prior venous thromboembolism, and non-intracranial, non-gastrointestinal bleedings were associated with the highest risk of discontinuation of oral anticoagulation (**Table 3**).

Table 4 presents the adjusted HRs and corresponding 95% CIs of treatment discontinuation of NOACs relative to VKAs. NOAC users were 55% less likely to discontinue their treatment than VKA users, which corresponds to more than a doubling of the probability of treatment persistence in NOAC users (HR 2.22, 95% CI 2.13-2.27). The median treatment persistence among those diagnosed in or after January 2011 was 12 months for VKA initiators and 43 months for NOAC initiators. **Figure 2** shows that 3 years after treatment initiation, 54% of patients receiving NOACs were persistent compared to 25% of patients receiving VKAs. In patients initiating VKAs before 2011, the probability of treatment persistence after 3 years was 29%, while the median treatment persistence was 14 months.

The results remained consistent in our sensitivity analyses. After applying different grace periods, the rates of treatment persistence after 3 years were higher with NOACs as compared with VKAs (grace period 60 days: 65% for NOACs versus 39% for VKAs; grace period 50% of the duration of the last prescription: 30% for NOACs versus 7% for VKAs). Moreover, after defining switchers from VKAs to NOACs and vice versa as continuous users of the initial treatment, treatment persistence after 3 years remained the same for both initial NOAC (54%) and VKA

(25%) users as compared to the main analysis.

DISCUSSION

This observational population-based cohort study of NVAF patients identified factors associated with treatment initiation with NOACs, and with treatment switching from VKAs to NOACs. Moreover, it provided an in-depth analysis of long-term treatment persistence among oral anticoagulant users.

In line with previous studies, we observed an underuse of oral anticoagulants in our cohort, since every second NVAF patient did not initiate NOACs or VKAs during the study period.[7,25] Of note, among initiators of oral anticoagulants previously receiving antiplatelet drugs, 14% of NOAC users and 27% of VKA users continued their antiplatelet treatment after initiating oral anticoagulation (defined as 2 or more antiplatelet prescriptions in the 3 months following initiation of anticoagulant). Although VKA initiators slightly outnumbered NOAC initiators overall, there was an increasing tendency towards NOAC initiation after 2011, which agrees with recent studies from other countries.[11,26,27] Moreover, our data showed that patients of advanced age with a CHA_2DS_2-VASc score ≥ 2 were less likely to initiate NOACs. Given the underrepresentation of very old, high-risk patients in clinical trials,[28-30] these findings could reflect the reluctance of physicians to prescribe NOACs in this population. Patients with chronic kidney disease were also less likely to initiate NOACs, indicating that the primarily renal clearance of NOACs leads physicians to prefer VKAs in case of impaired kidney function to avoid drug accumulation and increased toxicity risks.[11,31]

We observed that 27% of the VKA initiators in our cohort switched from VKAs to NOACs during follow-up, with the percentage for NOAC-to-VKA switchers being 5%. To date, reported rates of switching among groups of oral anticoagulants vary considerably.[11,32] To our knowledge,

our study is the first to systematically assess predictors of switching from initial VKA treatment to NOACs. Its findings highlight the influence of pharmacokinetics in this regard, since patients with chronic kidney disease were less likely to switch from VKAs to the predominantly renally excreted NOACs, and patients with liver disease were more likely to switch from the biliary excreted VKAs to NOACs.[4]

We also observed that advanced age and high thromboembolic risk were associated with a decreased risk of anticoagulant treatment discontinuation, i.e., a higher probability of treatment persistence, corroborating thus previous studies.[10,22] NOAC users had a 55% reduced risk of treatment discontinuation as compared to VKA users, and treatment persistence with NOACs was considerably higher than with VKAs after the first 3 years (54% versus 25%), which is congruent with published data[5,11] and compatible with the simpler use of NOACs as compared to VKAs. Importantly, most of the previous studies on anticoagulant treatment persistence had a maximum follow-up of up to 2 years.[5] As patterns of persistence can change over time,[33] our findings corroborate recently published data[11] showing a higher persistence with NOACs as compared to VKAs also in the long term. Finally, since persistence with VKAs in pre-2011 initiators of the 'VKA only' era was similar to that in post-2011 initiators, introducing NOACs seems to have doubled treatment persistence with oral anticoagulants among NVAF patients in Quebec.

Our study has several strengths. First, it is based on one of the largest and most recent population-based cohorts of NVAF patients, which enables the generalization of its results to NVAF patients from similar health care systems, and the calculation of precise and contemporary estimates for different aspects of utilization of oral anticoagulants in a real-world setting. Second, it is the first to concomitantly assess predictors of anticoagulant treatment initiation, treatment

switch and treatment discontinuation, while having one of the longest follow-up periods. Finally, by considering also the pre-2011 period, we were able to compare anticoagulant treatment persistence in NVAF in Quebec before and after the introduction of NOACs.

Our study also has some limitations. First, it is likely that the initiation of oral anticoagulation could have occurred in hospital prior to discharge, but the RAMQ does not contain data on inpatient prescriptions. However, it is expected that patients initiating anticoagulation therapy would be closely followed in the outpatient setting after hospital discharge, minimizing this potential exposure misclassification. Second, data on lifestyle risk factors including smoking or obesity are not available in the RAMQ. Thus, their impact on oral anticoagulant treatment could not be evaluated. Finally, the study was underpowered to assess predictors of switching from NOACs to VKAs.

In summary, an increasing number of newly diagnosed NVAF patients in Quebec receive NOACs as the initial oral anticoagulation, but advanced age and high thromboembolic risk are associated with a lower probability of initiating NOACs compared to VKAs. Pharmacokinetics influence both treatment initiation and switching in oral anticoagulation. Finally, NVAF patients on NOACs show a higher long-term treatment persistence than patients on VKAs, and the introduction of NOACs has doubled treatment persistence. Drug utilization studies with even longer follow-up could help further corroborate these findings.

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CONFLICT OF INTEREST

Professor Suissa has received research grants from Bayer Pharma, Boehringer Ingelheim, and Bristol-Myers-Squibb, and has participated in advisory board meetings or as speaker for AstraZeneca, Boehringer Ingelheim, and Novartis. Dr. Douros, Dr. Renoux and Ms Coulombe do not have any conflicts of interest to disclose.

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Table 1. Odds ratios of treatment initiation with NOACs relative to treatment initiation with VKAs by patient characteristics in patients diagnosed with NVAF in or after January 2011

	Initiating NOACs	Initiating VKAs	Crude OR	Adjusted* OR (95% CI)
Number of patients	14,746	17,685		
Age, mean (SD)	75.07 (9.18)	76.78 (9.07)		
40-49	0.89%	0.63%	1.00	1.00 (Reference)
50-59	3.69%	2.81%	0.93	0.94 (0.68-1.28)
60-69	20.43%	14.60%	0.99	1.03 (0.77-1.38)
70-79	40.12%	34.90%	0.81	0.87 (0.66-1.16)
≥80	34.88%	47.06%	0.52	0.55 (0.41-0.73)
Male sex	49.61%	48.53%	1.04	1.04 (0.99-1.10)
Calendar year of NVAF diagnosis				
2011	14.43%	33.79%	1.00	1.00 (Reference)
2012	19.21%	31.05%	1.45	1.72 (1.60-1.85)
2013	30.38%	22.34%	3.18	4.78 (4.44-5.14)
2014	35.98%	12.81%	6.58	9.09 (8.40-9.84)
Time from NVAF diagnosis to treatment initiation				
0-14 days	70.17%	78.90%	1.00	1.00 (Reference)
15-30 days	5.95%	5.94%	1.13	1.00 (0.90-1.11)
31-60 days	4.86%	4.43%	1.23	1.23 (1.09-1.39)
61-90 days	2.40%	2.14%	1.26	1.38 (1.16-1.63)
91-180 days	4.16%	2.72%	1.72	2.20 (1.91-2.52)
181-365 days	4.12%	2.56%	1.81	2.56 (2.22-2.95)
>365 days	8.33%	3.31%	2.83	6.24 (5.54-7.03)
Inpatient NVAF diagnosis	23.10%	43.13%	0.40	0.86 (0.80-0.92)
Cardiovascular comorbidities				
Arterial hypertension	45.23%	57.87%	0.60	0.98 (0.93-1.04)
Myocardial infarction	7.28%	17.25%	0.38	0.54 (0.50-0.59)
Diabetes mellitus	25.0%	32.48%	0.69	0.80 (0.75-0.84)
Venous thromboembolism	2.83%	7.41%	0.36	0.46 (0.41-0.52)
Congestive heart failure	9.86%	19.52%	0.45	0.76 (0.70-0.82)
Ischemic stroke	5.05%	7.77%	0.63	0.89 (0.80-0.99)
Vascular disease	4.73%	10.94%	0.40	0.69 (0.62-0.76)

	Initiating NOACs	Initiating VKAs	Crude OR	Adjusted* OR (95% CI)
Prior bleeding events				
Intracranial hemorrhage	0.99%	1.45%	0.68	0.86 (0.68-1.10)
Gastrointestinal hemorrhage	2.32%	3.32%	0.69	0.93 (0.79-1.09)
Other bleeding events	4.64%	7.93%	0.56	0.83 (0.74-0.93)
Blood dyscrasias	1.17%	3.36%	0.34	0.58 (0.48-0.70)
Predisposition to falls	8.97%	13.10%	0.65	0.96 (0.89-1.05)
Dementia or schizophrenia	4.96%	7.75%	0.62	0.95 (0.85-1.06)
Chronic kidney disease	4.30%	16.06%	0.23	0.35 (0.32-0.39)
Liver disease	1.27%	2.40%	0.53	0.77 (0.63-0.94)
Cancer	14.33%	15.60%	0.91	0.96 (0.90-1.03)
Prior use of ASA	33.79%	28.05%	1.31	1.10 (1.04-1.17)
Prior use of clopidogrel	5.02%	5.97%	0.83	0.88 (0.79-0.98)
CHA_2DS_2-VASc**				
0	2.75%	1.44%	1.00 (Reference)	
1	11.32%	6.08%	0.97 (0.82-1.16)	
≥2	85.94%	92.48%	0.49 (0.42-0.57)	

* Adjusted for all variables listed in the table except for the CHA_2DS_2-VASc categories.
** Risk estimates for the CHA_2DS_2-VASc categories were calculated in a separate model.

NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists; NVAF = non-valvular atrial fibrillation; SD = standard deviation; ASA = acetylsalicylic acid; CHA_2DS_2-VASc = **c**ongestive heart failure, arterial **h**ypertension, **a**ge ≥ 75 (doubled), **di**abetes mellitus, **s**troke (doubled), **v**ascular disease, **a**ge 65-74, **s**ex **c**ategory: female sex; OR = odds ratio; CI = confidence interval

Table 2. Hazard ratios of switching from initial VKA treatment to a NOAC by patient characteristics in patients diagnosed with NVAF in or after January 2011

	Remain on VKAs	Switch to NOACs	Crude HR	Adjusted* HR (95% CI)
Number of patients	12,922	4763		
Age, mean (SD)	78.6 (9.3)	76.0 (8.6)		
40-49	0.68%	0.48%	1.00	1.00 (Reference)
50-59	2.65%	3.25%	1.58	1.61 (1.04-2.49)
60-69	13.12%	18.60%	1.70	1.60 (1.05-2.46)
70-79	32.72%	40.81%	1.59	1.49 (0.96-2.31)
≥80	50.83%	36.85%	1.11	1.05 (0.67-1.65)
Male sex	48.83%	47.70%	0.97	1.03 (0.88-1.21)
Calendar year of NVAF diagnosis				
2011	31.57%	39.83%	1.00	1.00 (Reference)
2012	30.79%	31.77%	1.05	1.09 (1.02-1.17)
2013	22.98%	20.62%	1.33	1.46 (1.34-1.58)
2014	14.66%	7.79%	1.57	1.69 (1.50-1.91)
Time from NVAF diagnosis to VKA initiation				
0-6 months	93.58%	95.65%	1.00	1.00 (Reference)
6 months-1 year	2.68%	2.23%	0.99	1.00 (0.83-1.22)
1-2 years	2.43%	1.47%	0.85	0.93 (0.73-1.18)
2-4 years	1.32%	0.65%	1.05	1.21 (0.85-1.73)
Inpatient NVAF diagnosis	44.73%	38.78%	0.79	1.02 (0.95-1.10)
Cardiovascular comorbidities				
Arterial hypertension	58.83%	55.26%	0.86	1.06 (0.95-1.18)
Myocardial infarction	19.11%	12.20%	0.67	0.73 (0.66-0.80)
Diabetes mellitus	33.40%	29.98%	0.91	0.99 (0.89-1.10)
Venous thromboembolism	8.47%	4.53%	0.57	0.58 (0.50-0.67)
Congestive heart failure	21.07%	15.31%	0.79	1.01 (0.89-1.14)
Ischemic stroke	7.85%	7.54%	0.96	1.12 (0.91-1.38)
Vascular disease	12.06%	7.92%	0.71	0.81 (0.67-0.97)
Prior bleeding events				

	Remain on VKAs	Switch to NOACs	Crude HR	Adjusted* HR (95% CI)
Intracranial hemorrhage	1.55%	1.20%	0.88	0.97 (0.74-1.27)
Gastrointestinal hemorrhage	3.54%	2.73%	0.84	0.96 (0.81-1.15)
Other bleeding events	8.28%	6.97%	0.88	1.04 (0.93-1.18)
Blood dyscrasias	3.64%	2.60%	0.77	0.92 (0.76-1.10)
Predisposition to falls	14.06%	10.50%	0.80	0.94 (0.86-1.04)
Dementia or schizophrenia	8.63%	5.35%	0.79	0.98 (0.86-1.11)
Chronic kidney disease	19.05%	7.96%	0.47	0.53 (0.48-0.59)
Liver disease	2.41%	2.35%	1.10	1.30 (1.07-1.57)
Cancer	16.13%	14.15%	0.95	0.98 (0.90-1.06)
CHA_2DS_2-VASc**				
0	1.33%	1.72%	1.00 (Reference)	
1	5.44%	7.83%	1.10 (0.87-1.40)	
≥2	93.23%	90.45%	0.83 (0.67-1.04)	

* Adjusted for all variables listed in the table except for the CHA_2DS_2-VASc categories.
** Risk estimates for the CHA_2DS_2-VASc categories were calculated in a separate model.

VKAs = vitamin K antagonists; NOACs = non-vitamin K antagonist oral anticoagulants; NVAF = non-valvular atrial fibrillation; SD = standard deviation; CHA_2DS_2-VASc = **c**ongestive heart failure, arterial **h**ypertension, **a**ge ≥ 75 (doubled), **d**iabetes mellitus, **s**troke (doubled), **v**ascular disease, **a**ge 65-74, female **s**ex; HR = hazard ratio; CI = confidence interval

Table 3. Hazard ratios of discontinuation of anticoagulation treatment by patient characteristics in patients diagnosed with NVAF in or after January 2011

	Continuous treatment	Treatment discontinuation	Crude HR	Adjusted HR* (95% CI)
Number of patients	14,849	17,582		
Treatment initiation with NOACs vs VKAs	60.38%	27.85%	0.47	0.45 (0.44-0.47)
Age, mean (SD)	77.27 (9.06)	76.15 (9.33)		
40-49	0.52%	1.01%	1.00	1.00 (Reference)
50-59	2.66%	3.87%	0.71	0.74 (0.62-0.88)
60-69	16.43%	18.22%	0.56	0.59 (0.50-0.69)
70-79	36.91%	37.70%	0.53	0.54 (0.46-0.63)
≥80	43.48%	39.20%	0.49	0.47 (0.40-0.55)
Male sex	47.22%	51.16%	1.15	1.10 (1.06-1.14)
Calendar year of NVAF diagnosis				
2011	16.56%	34.97%	1.00	1.00 (Reference)
2012	20.95%	31.26%	0.92	0.97 (0.94-1.01)
2013	27.64%	24.05%	0.81	1.01 (0.96-1.06)
2014	34.86%	9.72%	0.66	0.93 (0.87-0.99)
Time from NVAF diagnosis to treatment initiation				
0-14 days	73.35%	76.82%	1.00	1.00 (Reference)
15-30 days	6.08%	5.79%	0.99	1.04 (0.97-1.11)
31-60 days	4.86%	4.35%	0.93	0.98 (0.90-1.07)
61-90 days	2.21%	2.31%	1.00	1.08 (0.96-1.21)
91-180 days	3.41%	3.33%	0.95	1.09 (0.99-1.20)
181-365 days	3.28%	3.25%	1.03	1.16 (1.05-1.29)
>365 days	6.81%	4.14%	0.93	1.13 (1.03-1.24)
Inpatient NVAF diagnosis	29.57%	39.29%	1.13	0.98 (0.94-1.02)
Cardiovascular comorbidities				
Arterial hypertension	49.98%	54.66%	1.01	0.96 (0.92-0.99)
Myocardial infarction	10.83%	14.95%	1.30	1.16 (1.11-1.22)
Diabetes mellitus	28.83%	29.38%	0.99	0.90 (0.87-0.93)
Venous thromboembolism	4.29%	6.55%	1.35	1.13 (1.05-1.21)
Congestive heart failure	14.21%	16.21%	1.13	1.00 (0.95-1.05)

	Continuous treatment	Treatment discontinuation	Crude HR	Adjusted HR* (95% CI)
Ischemic stroke	6.53%	6.53%	0.89	0.86 (0.80-0.92)
Vascular disease	7.22%	9.17%	1.16	1.01 (0.96-1.08)
Prior bleeding events				
Intracranial hemorrhage	1.33%	1.14%	0.91	0.96 (0.82-1.12)
Gastrointestinal hemorrhage	2.62%	3.15%	1.19	1.07 (0.97-1.17)
Other bleeding events	5.49%	7.54%	1.28	1.13 (1.06-1.21)
Blood dyscrasias	1.94%	2.86%	1.28	1.06 (0.96-1.17)
Predisposition to falls	11.27%	11.17%	0.99	0.95 (0.90-1.00)
Dementia or schizophrenia	7.01%	5.86%	0.94	0.95 (0.89-1.02)
Chronic kidney disease	10.04%	11.52%	1.12	0.93 (0.88-0.98)
Liver disease	1.64%	2.18%	1.30	1.12 (1.00-1.25)
Cancer	14.49%	15.65%	1.15	1.11 (1.06-1.16)
Prior use of ASA	16.21%	13.98%	0.94	0.94 (0.89-1.00)
Prior use of clopidogrel	2.93%	2.67%	1.04	1.01 (0.90-1.12)
CHA_2DS_2-VASc**				
0	1.61%	2.53%	1.00 (Reference)	
1	8.25%	8.72%	0.75 (0.67-0.84)	
≥2	90.14%	88.75%	0.64 (0.57-0.70)	

* Adjusted for all variables listed in the table except for the CHA_2DS_2-VASc categories.
** Risk estimates for the CHA_2DS_2-VASc categories were calculated in a separate model.

NVAF = non-valvular atrial fibrillation; NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists; SD = standard deviation; ASA = acetylsalicylic acid; CHA_2DS_2-VASc = **c**ongestive heart failure, arterial **h**ypertension, **a**ge ≥ 75 (doubled), **di**abetes mellitus, **s**troke (doubled), **v**ascular disease, **a**ge 65-74, **s**ex **c**ategory: female sex; HR = hazard ratio; CI = confidence interval

Table 4. Hazard ratios of discontinuation of NOAC treatment relative to VKA treatment in patients with NVAF diagnosed in or after January 2011 for different grace periods

	Crude HR	Adjusted* HR (95% CI)
Grace period of 30 days	0.47	0.45 (0.44-0.47)
Grace period of 60 days	0.65	0.61 (0.57-0.64)
Grace period of 50%	0.41	0.42 (0.41-0.44)

* Adjusted for age, sex, calendar year of NVAF diagnosis, time from NVAF diagnosis to treatment initiation, inpatient NVAF diagnosis, arterial hypertension, myocardial infarction, diabetes mellitus, venous thromboembolism, congestive heart failure, ischemic stroke, vascular disease, intracranial hemorrhage, gastrointestinal hemorrhage, other bleeding events, blood dyscrasias, predisposition to falls, dementia or schizophrenia, chronic kidney disease, liver disease, cancer, and prior use of acetylsalicylic acid or clopidogrel.

NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists; NVAF = non-valvular atrial fibrillation; HR = hazard ratio; CI = confidence interval

FIGURE LEGENDS

Figure 1. Flowchart of study cohort formation

AF = atrial fibrillation; NVAF = non-valvular atrial fibrillation; RAMQ = Canadian Province of Quebec's health insurance databases; t0 = date of the first inpatient or outpatient NVAF diagnosis

Figure 2. Kaplan-Meier curves for probability of persistence in the first 3 years after treatment initiation with NOACs compared with VKAs for patients diagnosed with NVAF in or after January 2011

NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists; NVAF = non-valvular atrial fibrillation

Figure 1

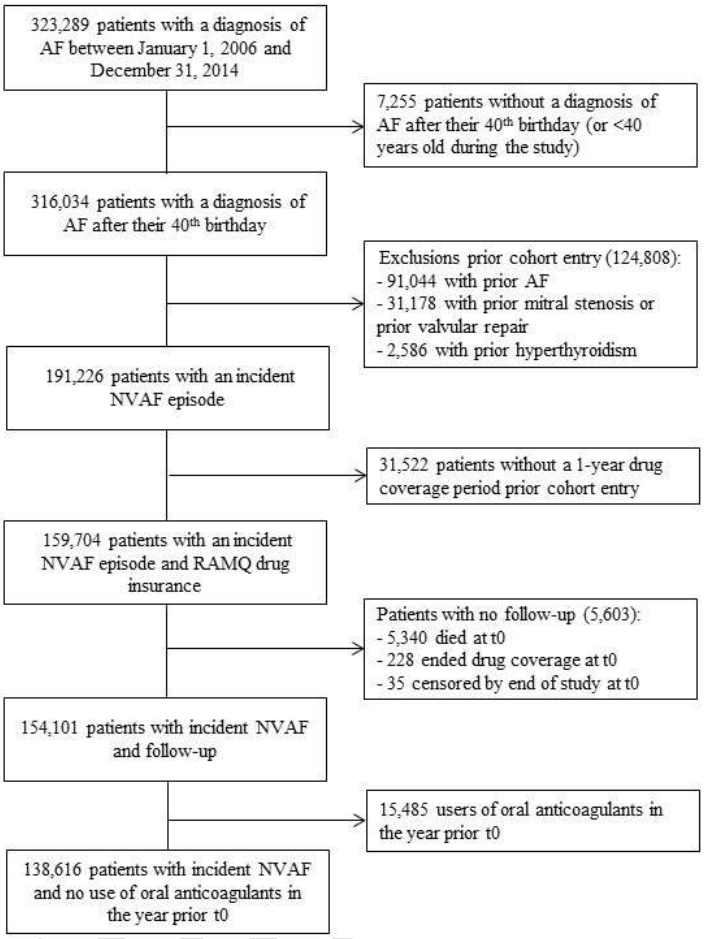
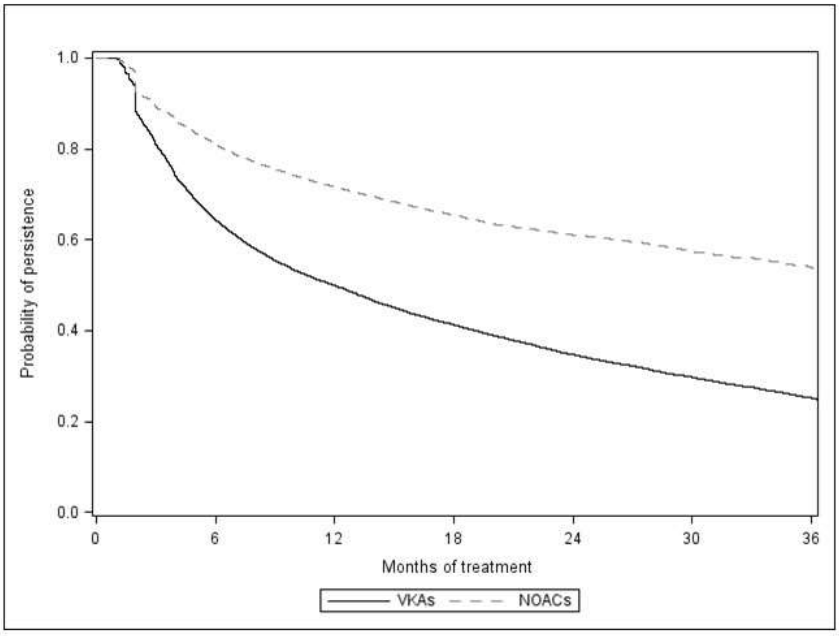


Figure 2


1.0
0.8
0.6
0.4
0.2
0.0
Probability of persistence
0
6
12
18
24
30
36
Months of treatment
VKAs
NOACs