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ORIGINAL ARTICLE

Trends of use and factors that determine the choice of oral anticoagulants in women and men with atrial fibrillation

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Abstract

The aim was to identify sex-specific factors linked with oral anticoagulant initiation in a cohort of patients with atrial fibrillation using administrative data from Quebec (Canada) between 2014 and 2017. Cohort entry defined as new users, that is, no claims in last 12 months, a cohort of 32 050 patients was stratified in two groups, that is, women and men. Multivariable regression models were used to identify factors of initiations for low- and standard-dose direct oral anticoagulants (DOACs) versus warfarin, and low- versus standard-dose DOACs. In both sexes, warfarin initiation decreased and DOAC initiation increased, with year of initiation as major factors of DOACs use. In 2017, the increase was of 2- to 4-fold and 3- to 8-fold for low- and standard-dose DOACs (vs. warfarin), respectively. The proportion of patients starting on a low-dose DOAC was higher in women than men. Older age for both sexes and $CHADS_2$ score ≥2 (only women) were major factors of low-dose dabigatran and rivaroxaban versus warfarin use. The only significant factor of standard-dose DOAC versus warfarin use was age of 65–79 for women or men treated with apixaban by 1.8- and 1.4-fold, respectively. Factors that made women and men less likely to receive a standard-dose DOAC versus warfarin were higher $CHADS_2$ (for dabigatran and rivaroxaban), HAS-BLED and frailty scores, prior coronary disease, major bleeding, and chronic kidney disease (CKD) status. The choice of a low- versus standard-dose DOAC was mainly driven by age and CKD, and higher $CHADS_2$ score (for dabigatran and apixaban) for both sexes.

KEYWORDS
anticoagulants, atrial fibrillation, oral administration, pharmacoepidemiology, prescription drugs

Abbreviations: AF, atrial fibrillation; aOR, adjusted odds ratio; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases; OAC, oral anticoagulant; RAMQ, *Régie de l'Assurance Maladie du Québec*; SD, standard deviation.

1 | INTRODUCTION

Sex-specific differences have been observed in the epidemiology of atrial fibrillation (AF) (i.e., a lower prevalence and later onset in women), its pathophysiology (i.e., sex-related differences in AF triggers and substrates), and its clinical presentation (i.e., women are more likely to be symptomatic and have more severe symptoms).[1,2] With a view to developing sex-specific recommendations, the European and Canadian Society of Cardiology's 2020 guidelines on the diagnosis and management of AF emphasized the importance of reporting sex-specific analyses of the efficacy and safety of preventive interventions.[3,4]

The literature data have highlighted sex-specific differences in the quality and efficacy of oral anticoagulant (OAC) treatment.[5,6] The stroke risk (as evaluated by the CHA_2DS_2-VASc score) is significantly higher for women with AF than for their men counterparts, regardless of the age and comorbidity profile in contrast to the $CHADS_2$ score.[5,7–9] Regardless or not of the CHA_2DS_2-VASc score, however, it has been reported that women are significantly less likely to receive OACs.[10–12] A recent publication demonstrated that in real life (and in contrast to the data from randomized clinical trials), women with AF are more likely to receive low-dose direct oral anticoagulants (DOACs) than standard-dose DOACs.[13] And, the net benefit of low-dose DOACs compared to warfarin seems to vary from one DOAC to another.[14] Again, a recent systematic review of observational studies versus randomized clinical trials, the higher risk profiles of AF patients in clinical practice treated with apixaban 2.5 mg (vs. 5 mg) may explain (i) the higher-than-expected thromboembolic event, major bleeding, and mortality rates in the clinic.[15] So, it is not yet clear whether (i) this sex-specific difference in OAC use is due to the comorbidity profile, the fragility profile, or to concomitant medications, and (ii) DOAC dose reduction is appropriate or not.

The 2018 American College of Chest Physicians Guideline and Expert Panel Report gave recommendations on DOACs for various subgroups of patients with AF.[16] For instance, based on expert opinion, standard-dose of dabigatran is recommended for patients with recurrent thrombosis events, and apixaban is recommended for patients at high risk of gastrointestinal bleeding. Furthermore, the European 2021 guidelines maintained that the DOAC dose should be selected as a function of the patient's age, renal function, weight, concomitant medications, and body mass index.[3] Prescribing an OAC for AF should be individualized and should take account of the patient's clinical history and preferences. However, a recent systematic review of observational studies reported that close to 50% of patients receiving low-dose apixaban do not meet at least two of three clinical characteristics (age ≥ 80, creatinine ≥1.5 mg/dl, and body weight ≤ 60 kg).[15] Giving the paucity of data assessing the factors associated with the initiation of OAC prescriptions among women and men, according to the specific agent and the dose selection, further research is therefore needed to assess prescribing patterns for individual DOACs and warfarin, and also the factors associated with dose selection in clinical practice where there are no potential barriers for prescribers.

Thus, the primary objective of the present observational study was to assess the trend of use from 2014 to 2017, and to identify demographic and clinical factors including $CHADS_2$ and HAS-BLED scores of low-dose DOACs (dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily and apixaban 2.5 mg twice daily) and standard-dose DOACs (dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily and apixaban 5 mg twice daily) initiation versus warfarin initiation, and low-dose versus standard-dose DOACs initiation among women and men in a cohort of AF patients treated in Quebec, Canada.

2 | MATERIAL AND METHODS

2.1 | Data source

We built a cohort of patients with AF from administrative databases (hospital discharge data from Med-Echo and the *Régie de l'Assurance Maladie du Québec* [RAMQ] medical services; and RAMQ public drug plan) administered by the RAMQ (Table S1).[17–19] The databases were linked through encrypted health insurance numbers; together, they provided a complete picture of hospital admissions. The protocol was approved by an institutional review board (University of Montreal).

2.2 | The population-based cohort

We conducted a retrospective analysis of prescription claims between January 1, 2014, and December 31, 2017, by adult patients (≥18 years of age) diagnosed with AF (according to the International Classification of Diseases [ICD]-9 codes 427.3, 427.31 or 427.32, or the ICD-10 code I48).[20] Previous validation studies have shown that ICD-9 codes identify cases of AF accurately, with a median positive predictive value of at least 89%.[21]

Thereafter, we stratified the cohort into sub-groups, that is, women and men. We then identified women and men who received a new prescription of apixaban (2.5 or 5 mg), dabigatran (110 and 150 mg), rivaroxaban (15 or 20 mg), or warfarin over the period 2014–2018. We considered only new users, that is, users with no OAC prescriptions in the 12 months preceding the index prescription. The baseline period was defined for patients who had pharmacy coverage for 12 months and were continually enrolled in an insurance drug plan for at least 1 year before the index date. The AF had to be diagnosed in the 12 months prior to OAC initiation.

We excluded patients diagnosed with deep venous thrombosis or pulmonary embolism (as a primary or secondary diagnosis) in the year preceding the claim date index. We next excluded patients having undergone cardiac valve replacement in the 5 years before cohort entry, and those with end-stage chronic kidney disease (CKD), a kidney transplant, or dialysis for at least 3 months in the 3 years before cohort entry. Patients with a coagulation deficiency in the 3 years preceding the index date were subsequently excluded. Lastly, we excluded patients having undergone hip or knee replacement surgery

in the 6 weeks prior to the index date or certain medical procedures (cardiac catheterization, stent placement, coronary artery bypass graft, cerebrovascular procedures, valve replacement procedures, or defibrillator placement) in the 3 months prior to the index date.

2.3 | Outcomes

The primary outcome was the choice of OAC (warfarin, low-dose DOAC, or standard-dose DOAC) initiated, according to the first claim on the index date.

2.4 | Factors of OAC choice at treatment initiation

The demographic and clinical factors of drug choice initiation considered here were age group (65–79 vs. ≥80 vs. <65), the $CHADS_2$ score (≥2 vs. <2), the HAS-BLED score (≥3 vs. <3), frailty score (≥9 vs. <9), coronary artery disease (CAD) (including myocardial infarction), stroke (including transient ischemic attack), major bleeding, antiplatelet agent use (including acetylsalicylic acid use), and CKD.

2.5 | Demographic and clinical characteristics of the study population

Whereas demographic variables were recorded at cohort entry, comorbidities were evaluated during the 3 years preceding the index date. We used the patients' characteristics and associated comorbidities to assess the $CHADS_2$ score and the modified HAS-BLED score[22–24] within the 3 years preceding the index date (Tables S2–S4). The Charlson-Deyo Comorbidity Index was considered as a marker of comorbidities[25,26] and was also evaluated within the 3 years preceding the index date. We also determined a frailty score; this was an adaptation of the Elders Risk Assessment Index, which rates multidimensional risk factors (with social, psychological, biological, clinical, cognitive, and environmental components) over the 2 years prior to cohort entry (Table S5).[27,28] Finally, CKD was determined using a validated algorithm.[29] CKD stage was defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist (as identified in the administrative databases). This composite variable has been validated, with reference to medical chart reviews of older adults with CKD (the algorithm used for estimated glomerular filtration rate [eGFR] definition had a positive predictive value ranging from 94.5% to 97.7%).

Lastly, we assessed prescriptions filled in the one-month preceding cohort entry. Many of the medications were investigated because they are known to interact with OACs (Table S6).[30–32] But, giving the low prevalence of major drug interactions, they were not assessed as determinants of OAC use (Tables 3–5; Tables S7–S9). Although data on aspirin fulfillments were recorded, unaccounted-for over-the-counter use may limit the value of this variable. The physician who prescribed the OAC at the index date was classified as a cardiologist, a primary care physician, or another type of physician.

2.6 | Statistical analyses

To illustrate time trends in OAC use by men and by women, we plotted the number of claims per year from 2014 to 2017. We used descriptive statistics to summarize the patients' demographic and clinical characteristics as a function of the initiated OAC and the sex. The association between the factors at the baseline and the initiation of a DOAC was analyzed using a multivariable (adjusted) logistic regression calculating adjusted odds ratios (aORs) and associated 95% confidence intervals (CIs) among women and men. The models were as follows: three models (dabigatran, rivaroxaban, apixaban) for the determinants of low-dose DOAC initiation versus warfarin (reference), three other models (dabigatran, rivaroxaban, apixaban) for the determinants of standard-dose DOAC initiation versus warfarin (reference), and finally three models for the determinants of low-dose initiation versus standard-dose DOAC. All these models were performed for women and for men. We also provided the univariable (crude) logistic regression for the analyses. All analyses were conducted using SAS software (version 9.4).

3 | RESULTS

3.1 | Overall time trends

A total of 32 050 patients (including 16 896 women, 53.0%) filled out a new OAC prescription between 2014 and 2017 (Figure 1). For both sexes, the proportion of patients starting on warfarin decreased during the study period (Figure 2). In 2017, the most frequently initiated drug was apixaban 5 mg (in 41.0% of women and 45.0% of men). In contrast to other DOACs, initiation with apixaban 5 mg doubled between 2014 and 2017.

3.2 | Baseline demographic and clinical characteristics of women with AF

Of the 16 896 women with AF (mean ± standard deviation [SD] age: 79.5 ± 9.1), 2925 (17.3%) started on warfarin, 4904 (29.0%) started on a low-dose DOAC, and 9067 (53.7%) started on a standard-dose DOAC. Women using warfarin were older (81.9 ± 9.3 years of age) than women using a standard-dose DOAC (between 71.4 ± 7.0 and 76.7 ± 8.0 years of age) (Table 1). In contrast, the mean ± SD $CHADS_2$ score (2.6 ± 1.3) and HAS-BLED score (3.1 ± 1.4) in women using warfarin were similar to those observed in women using a low-dose DOAC (2.3 ± 1.1 to 2.5 ± 1.1 and 2.3 ± 1.3 to 2.7 ± 1.3, respectively) but higher than those observed in women using a standard-dose DOAC (1.5 ± 1.2 to 2.0 ± 1.2 and 2.0 ± 1.1 to 2.4 ± 1.3, respectively). Among the women, the mean ± SD Charlson score was higher in warfarin users (4.4 ± 3.4) than in low-dose (between 2.8 ± 2.8 and 3.5 ± 3.1) and standard-dose (between 2.2 ± 2.8 and 3.0 ± 3.1) DOAC users.

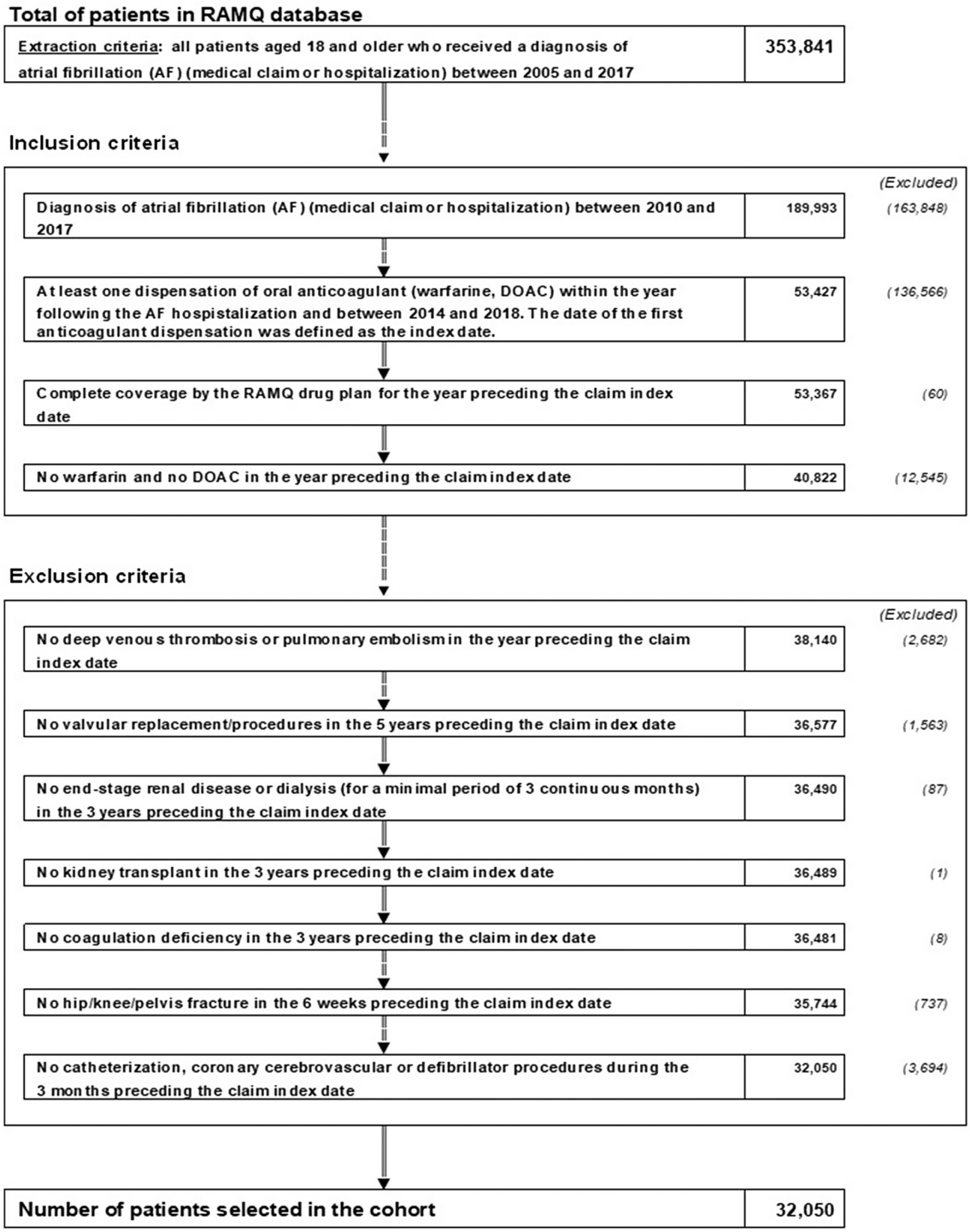

FIGURE 1 Study flowchart. AF, atrial fibrillation; DOACs, direct oral anticoagulants; RAMQ, *Régie de l'assurance maladie du Québec*.

On average, women using a low-dose DOAC were 10 years older than women using a standard-dose DOAC. The mean $CHADS_2$ score was higher in women using low-dose DOACs (between 2.3 and 2.5), than in women using standard-dose DOACs (between 1.5 and 2.0); the same was true for the HAS-BLED scores (2.3 to 2.7 and 2.0 to 2.4, respectively) and the Charlson scores (2.8 to 3.5 and 2.2 to 3.0, respectively). Medication use and healthcare service use of women are shown in Table S10.

3.3 | Baseline demographic and clinical characteristics of men with AF

Of the 15 154 men with AF (mean ± SD age: 75.9 ± 9.5) included in the study, 2360 (15.6%) started on warfarin, 2520 (16.6%) started on a low-dose DOAC, and 10 274 (67.8%) started on a standard-dose DOAC. Men using warfarin were older (78.7 ± 9.4 years of age) than men using a standard-dose DOAC (between 69.8 ± 7.4 and

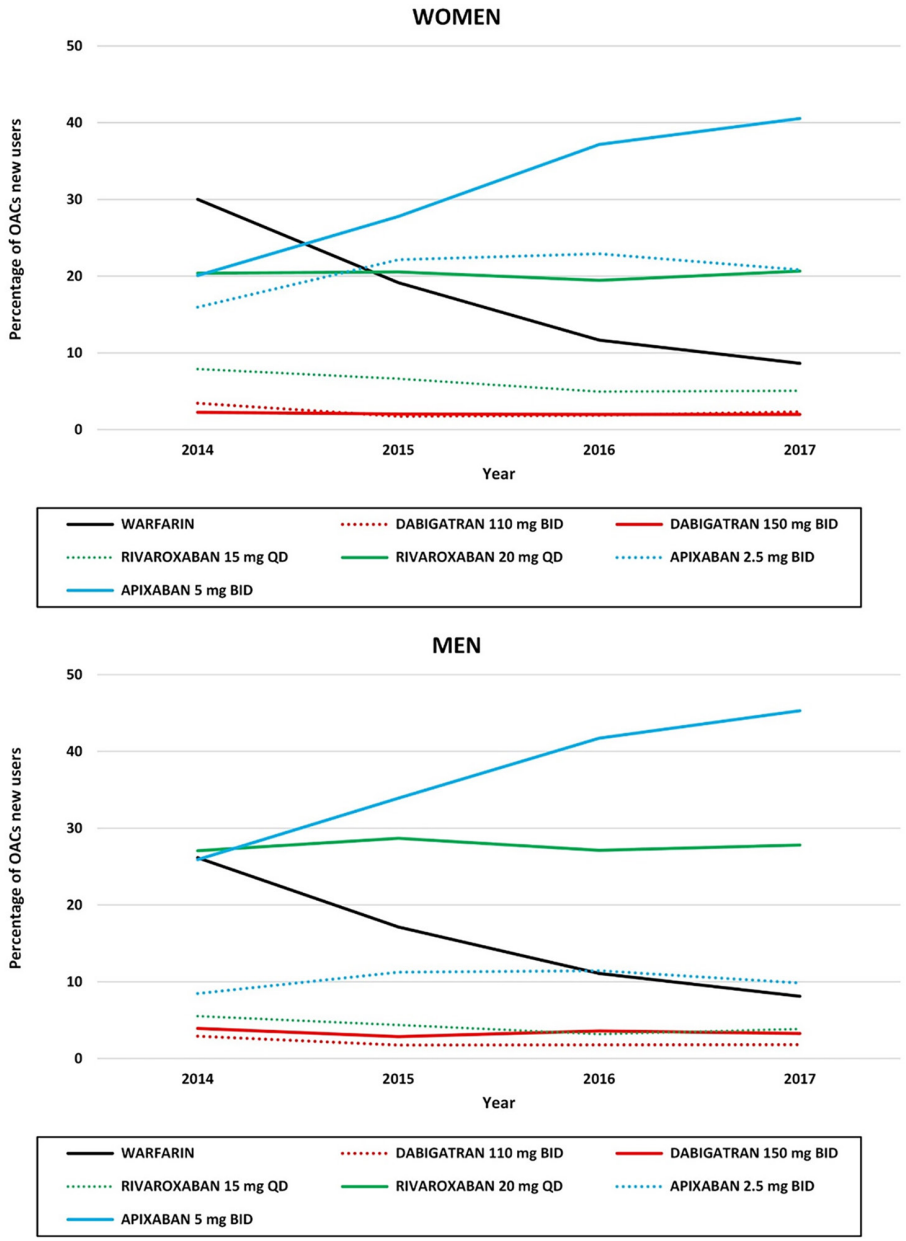

FIGURE 2 Changes in oral anticoagulant initiation from 2014 to 2017. BID, twice a day; OACs, oral anticoagulants; QD, once daily.

75.1 ± 8.6 years of age) (Table 2). In contrast, the mean ± SD $CHADS_2$ score (2.6 ± 1.3) and HAS-BLED score (3.1 ± 1.5) in men using warfarin slightly differ with regard to low-dose DOAC (2.3 ± 1.2 to 2.6 ± 1.2 and 2.4 ± 1.3 to 2.9 ± 1.4, respectively) but were substantially different from those using a standard-dose DOAC (1.4 ± 1.1 to 1.9 ± 1.3 and 1.8 ± 1.1 to 2.4 ± 1.3, respectively). Men using a low-dose DOAC and men using a standard-dose DOAC differ with regard to the mean $CHADS_2$ score or the mean HAS-BLED score. The mean ± SD Charlson score was higher in warfarin users (5.2 ± 3.8) than in low-dose (between 3.6 ± 3.6 and 4.8 ± 3.6) and standard-dose (between 2.7 ± 3.0 and 3.5 ± 3.3) DOAC users.

On average, men using a low-dose DOAC were 10 years older than men using a standard-dose DOAC. The mean $CHADS_2$ score was higher in men using low-dose DOACs (between 2.3 and 2.6), than in men using standard-dose DOACs (between 1.4 and 1.9); the same was true for the HAS-BLED scores (2.4 to 2.9 and 1.8 to 2.4, respectively) and the Charlson scores (3.6 to 4.8 and 2.7 to 3.5, respectively). Medication use and healthcare service use of men are shown in Table S11.

3.4 | Factors associated with DOAC versus warfarin

As shown in Table 3 (crude estimates in Tables S7–S8), one of the major factors of DOAC initiation versus warfarin among women was the year of initiation for low-dose DOAC and standard-dose DOAC, where the aORs ranged from 1.40 (95%CI 1.16–1.69) to 8.36 (95%CI

TABLE 1 Demographic and clinical characteristics of women new users of OACs ($n = 16896$)

		VKA ($n = 2925$)	Low-dose DOACs ($n = 4904$)			Standard-dose DOACs ($n = 9067$)		
	Total ($n = 16896$)	Warfarin ($n = 2925$)	Dabigatran 110 mg ($n = 387$)	Rivaroxaban 15 mg ($n = 1034$)	Apixaban 2.5 mg ($n = 3483$)	Dabigatran 150 mg ($n = 348$)	Rivaroxaban 20 mg ($n = 3410$)	Apixaban 5 mg ($n = 5309$)
Age, years (mean ± SD)	79.5 ± 9.1	81.9 ± 9.3	82.1 ± 7.1	83.4 ± 7.1	86.6 ± 5.9	71.4 ± 7.0	74.1 ± 8.3	76.7 ± 8.0
Age, years (median, Q_1–Q_3)	80.3 (73.3–86.3)	83.4 (76.1–88.8)	82.8 (78.0–87.1)	83.8 (79.1–88.4)	86.9 (83.1–90.7)	71.9 (67.9–75.5)	74.2 (68.9–79.7)	76.9 (71.7–82.1)
Age < 65	5.6%	4.9%	2.3%	1.0%	0.5%	13.8%	11.5%	6.1%
Age 65–79	43.2%	31.4%	32.6%	27.6%	9.1%	78.7%	64.6%	59.9%
Age ≥ 80	51.2%	63.7%	65.1%	71.5%	90.4%	7.5%	23.9%	34.1%
$CHADS_2$ score (mean ± SD)	2.2 ± 1.3	2.6 ± 1.3	2.3 ± 1.1	2.4 ± 1.1	2.5 ± 1.1	1.5 ± 1.2	1.6 ± 1.2	2.0 ± 1.2
$CHADS_2$ score < 2	30.2%	18.0%	21.5%	20.1%	15.7%	56.9%	50.2%	34.5%
$CHADS_2$ score ≥ 2	69.8%	82.0%	78.5%	79.9%	84.3%	43.1%	49.8%	65.5%
CHA_2DS_2-VASc score (mean ± SD)	3.6 ± 1.3	4.2 ± 1.4	3.7 ± 1.2	3.9 ± 1.1	4.1 ± 1.1	2.8 ± 1.2	3.0 ± 1.2	3.4 ± 1.3
CHA_2DS_2-VASc score < 3	18.3%	9.3%	8.0%	5.9%	1.7%	48.6%	37.3%	22.9%
CHA_2DS_2-VASc score ≥ 3	81.8%	90.7%	92.0%	94.1%	98.3%	51.4%	62.7%	77.1%
HAS-BLED score (mean ± SD)	2.5 ± 1.3	3.1 ± 1.4	2.3 ± 1.3	2.6 ± 1.3	2.7 ± 1.3	2.0 ± 1.3	2.0 ± 1.1	2.4 ± 1.3
HAS-BLED score < 3	57.1%	38.1%	63.6%	53.9%	47.8%	73.0%	75.1%	61.2%
HAS-BLED score ≥ 3	42.9%	61.9%	36.4%	46.1%	52.2%	27.0%	24.9%	38.8%
Charlson score (mean ± SD)	3.2 ± 3.2	4.4 ± 3.4	2.8 ± 2.8	3.2 ± 3.1	3.5 ± 3.1	2.3 ± 2.7	2.2 ± 2.8	3.0 ± 3.1
Charlson score <4	64.1%	45.7%	70.0%	63.1%	59.2%	79.3%	78.5%	67.1%
Charlson score ≥ 4	35.9% 2%	54.3%	30.0%	36.9%	40.8%	20.7%	21.6%	32.9%
Frailty score (mean ± SD)	12.4 ± 7.6	15.9 ± 7.3	11.8 ± 7.8	13.4 ± 7.4	15.3 ± 7.2	8.3 ± 6.5	8.8 ± 6.7	11.1 ± 7.2
Frailty score 0–3 (well)	16.5%	8.9%	19.1%	13.2%	7.6%	28.7%	27.4%	19.2%
Frailty score 4–8	19.9%	10.5%	24.0%	18.0%	15.7%	27.0%	28.8%	21.9%
Frailty score 9–15 (pre-frail)	24.9%	21.3%	21.7%	26.8%	23.6%	28.5%	24.4%	27.7%
Frailty score ≥ 16 (frail)	38.7%	59.3%	35.1%	42.1%	53.1%	15.8%	19.4%	31.2%

TABLE 1 (Continued)

		VKA (n = 2925)	Low-dose DOACs (n = 4904)			Standard-dose DOACs (n = 9067)		
	Total (n = 16896)	Warfarin (n = 2925)	Dabigatran 110 mg (n = 387)	Rivaroxaban 15 mg (n = 1034)	Apixaban 2.5 mg (n = 3483)	Dabigatran 150 mg (n = 348)	Rivaroxaban 20 mg (n = 3410)	Apixaban 5 mg (n = 5309)
Hypertension	72.7%	80.4%	72.9%	75.7%	77.4%	62.6%	63.0%	71.5%
Coronary artery disease	35.8%	49.0%	30.8%	36.9%	41.4%	27.6%	26.0%	31.9%
Acute myocardial infarction	8.9%	14.9%	8.3%	10.0%	11.5%	5.5%	4.6%	6.8%
Chronic heart failure	24.7%	39.7%	20.9%	25.2%	30.4%	8.6%	13.3%	21.3%
Cardiomyopathy	3.3%	4.1%	2.1%	3.0%	3.4%	2.6%	2.9%	3.4%
Other cardiac dysrhythmias	13.3%	14.7%	15.8%	12.4%	14.8%	8.1%	11.6%	12.9%
Valvular heart disease	14.2%	26.9%	12.7%	12.3%	17.1%	7.5%	7.9%	10.2%
Stroke/transient ischemic attack	13.0%	16.6%	12.9%	11.9%	14.5%	12.6%	8.2%	13.2%
Peripheral vascular (arterial) disease	11.9%	19.3%	12.7%	12.0%	14.1%	7.8%	6.6%	10.1%
Dyslipidemia	35.3%	43.2%	29.2%	35.3%	36.9%	26.4%	28.1%	35.4%
Diabetes	26.1%	31.8%	23.0%	25.5%	22.6%	26.7%	21.8%	28.4%
Major bleeding	19.7%	30.3%	19.6%	20.5%	24.0%	12.1%	11.2%	17.0%
Major intracranial bleeding	3.0%	4.0%	3.1%	2.8%	3.7%	2.3%	1.7%	2.8%
Major gastrointestinal bleeding	5.4%	6.9%	4.4%	5.7%	6.1%	4.0%	4.1%	5.1%
Other sites of major bleeding	13.9%	23.5%	14.5%	15.4%	17.9%	6.0%	6.4%	10.9%
Chronic kidney disease	22.6%	45.4%	12.9%	25.1%	30.0%	8.3%	7.9%	15.9%
Chronic kidney disease ≤30 ml/min	2.6%	8.7%	1.0%	1.5%	2.3%	0.0%	0.3%	1.4%
Acute renal failure	13.8%	30.0%	8.0%	13.9%	17.3%	4.3%	4.6%	9.5%
Liver disease	1.3%	1.5%	1.8%	1.0%	1.0%	2.0%	1.0%	1.5%
COPD/asthma	28.0%	32.6%	21.5%	27.8%	26.7%	27.6%	25.3%	28.6%
Helicobacter pylori infection	0.7%	0.9%	0.0%	1.1%	0.6%	0.9%	0.7%	0.6%
Depression	10.1%	10.1%	10.9%	11.0%	11.0%	8.3%	9.0%	10.1%

(Continues)

TABLE 1 (Continued)

	Total (n = 16896)	VKA (n = 2925)	Low-dose DOACs (n = 4904)			Standard-dose DOACs (n = 9067)		
		Warfarin (n = 2925)	Dabigatran 110 mg (n = 387)	Rivaroxaban 15 mg (n = 1034)	Apixaban 2.5 mg (n = 3483)	Dabigatran 150 mg (n = 348)	Rivaroxaban 20 mg (n = 3410)	Apixaban 5 mg (n = 5309)
Medical procedures								
Cardiac catheterization	2.2%	2.6%	0.8%	1.4%	2.2%	3.5%	1.8%	2.4%
Percutaneous coronary surgery—stent	1.4%	2.1%	1.6%	2.2%	1.4%	0.6%	1.0%	1.3%
Coronary artery bypass graft	0.2%	0.3%	0.0%	0.1%	0.2%	0.3%	0.2%	0.2%
For cerebrovascular disease	0.5%	0.9%	0.5%	0.8%	0.4%	0.6%	0.3%	0.4%

Abbreviations: COPD, chronic obstructive pulmonary disease; DOACs, direct oral anticoagulants; n, number of patients; OACs, oral anticoagulants; Q_1, first quartile; Q_3, third quartile; SD, standard deviation; VKA, vitamin K antagonist.

7.09–9.86). Women aged between 65 and 79 years (aOR 5.69, 95%CI 2.83–11.43) or 80 years or over (aOR 17.91, 95%CI 10.45–30.71) were more likely to receive low-dose of rivaroxaban and low-dose of apixaban than warfarin, respectively. Women with a $CHADS_2$ score ≥2 were more likely to receive low-dose of dabigatran (aOR 1.69, 95%CI 1.23–2.32) and rivaroxaban (aOR 1.26, 95%CI 1.01–1.58) than warfarin. In contrast, the only significant determinant of a standard-dose DOAC versus warfarin use was age group of 65–79 for only women treated with apixaban (aOR 1.84, 95%CI 1.45–2.34). The factors that made women less likely to receive a standard-dose DOAC versus warfarin were higher HAS-BLED and frailty scores, prior CAD, major bleeding, and CKD status.

As shown in Table 4 (crude estimates in Tables S7–S8), similar results were observed in men for the year of initiation for low-dose DOAC and standard-dose DOAC versus warfarin, where the aORs ranged from 1.52 (95%CI 1.17–1.97) to 7.04 (95%CI 5.92–8.36). Men aged between 65 and 79 years (aOR 3.16, 95%CI 1.49–6.73) or 80 years or over (aOR 13.77, 95%CI 8.15–23.26) were more likely to receive low-dose of dabigatran and low-dose of apixaban than warfarin, respectively. As in women, the only significant factor for standard-dose DOAC initiation versus warfarin was age 65–79 for only men treated with apixaban (aOR 1.40, 95%CI 1.13–1.73). The factors that made men less likely to receive a standard-dose versus warfarin were higher $CHADS_2$, HAS-BLED, and frailty scores, prior CAD, major bleeding, and CKD status.

3.5 | Factors associated with low-dose DOAC versus standard-dose DOAC

In contrast to the factors associated with the prescription of DOACs versus warfarin, men and women incident users were less likely to receive low-dose DOACs (vs. standard-dose DOACs) (Table 5; crude estimates in Table S9). In both sexes, the major factors for low- versus standard-dose DOAC initiation were age 80 and over. Women with a higher $CHADS_2$ score were more likely to receive a low dose of dabigatran (aOR 3.15, 95%CI 2.01–4.92) and rivaroxaban (aOR 1.28, 95%CI 1.04–1.58) than their respective standard-dose. Other factors that made women more likely to receive low dose of rivaroxaban and apixaban versus a standard dose were a higher frailty score, prior major bleeding, and CKD status. Men with a higher $CHADS_2$ score were more likely to receive a low dose of dabigatran (aOR 2.04, 95%CI 1.32–3.15) and rivaroxaban (aOR 1.32, 95%CI 1.04–1.68) than their respective standard-dose. Other factors that made men more likely to receive low dose of rivaroxaban and apixaban versus a standard dose were CKD status, and prior major bleeding for only apixaban.

4 | DISCUSSION

Warfarin and DOAC use changed between 2014 and 2017. In both sexes, warfarin use fell as DOAC use rose (mainly driven by apixaban).

TABLE 2 Demographic and clinical characteristics of men new users of OACs (n = 15 154)

		VKA (n = 2360)	Low-dose DOACs (n = 2520)			Standard-dose DOACs (n = 10 274)		
	Total (n = 15 154)	Warfarin (n = 2360)	Dabigatran 110 mg (n = 312)	Rivaroxaban 15 mg (n = 639)	Apixaban 2.5 mg (n = 1569)	Dabigatran 150 mg (n = 515)	Rivaroxaban 20 mg (n = 4188)	Apixaban 5 mg (n = 5571)
Age, years (mean ± SD)	75.9 ± 9.5	78.7 ± 9.4	81.2 ± 7.1	81.7 ± 7.6	84.6 ± 6.5	69.8 ± 7.4	71.8 ± 9.2	75.1 ± 8.6
Age, years (median, Q_1–Q_3)	76.2 (70.0–82.9)	79.7 (72.6–85.7)	81.8 (78.0–85.8)	82.9 (77.1–86.8)	85.3 (81.4–88.9)	70.3 (66.6–74.6)	72.3 (67.5–77.5)	75.3 (69.9–80.9)
Age < 65 years	10.0%	7.1%	2.6%	3.0%	1.1%	18.1%	16.5%	9.3%
Age 65–80 years	54.6%	43.8%	33.7%	33.5%	15.6%	75.9%	66.9%	62.6%
Age ≥ 80 years	35.4%	49.1%	63.8%	63.5%	83.4%	6.0%	16.6%	28.2%
$CHADS_2$ score (mean ± SD)	2.0 ± 1.3	2.6 ± 1.3	2.3 ± 1.3	2.3 ± 1.2	2.6 ± 1.2	1.4 ± 1.1	1.5 ± 1.2	1.9 ± 1.3
$CHADS_2$ score < 2	38.4%	21.0%	26.6%	24.6%	16.3%	60.0%	55.0%	39.8%
$CHADS_2$ score ≥ 2	61.6%	79.0%	73.4%	75.4%	83.7%	40.0%	45.0%	60.2%
CHA_2DS_2-VASc score (mean ± SD)	2.4 ± 1.4	3.0 ± 1.5	2.6 ± 1.2	2.8 ± 1.2	3.1 ± 1.2	1.6 ± 1.1	1.8 ± 1.2	2.3 ± 1.3
CHA_2DS_2-VASc score < 3	59.7%	38.7%	59.6%	49.1%	37.7%	82.3%	75.4%	62.1%
CHA_2DS_2-VASc score ≥ 3	40.3%	61.3%	40.4%	50.9%	62.3%	17.7%	24.6%	38.0%
HAS-BLED score (mean ± SD)	2.4 ± 1.4	3.1 ± 1.5	2.4 ± 1.3	2.6 ± 1.3	2.9 ± 1.4	1.8 ± 1.1	2.0 ± 1.2	2.4 ± 1.3
HAS-BLED score < 3	58.9%	38.2%	61.2%	52.1%	44.6%	78.6%	73.0%	59.9%
HAS-BLED score ≥ 3	41.1%	61.8%	38.8%	47.9%	55.4%	21.4%	27.0%	40.1%
Charlson score (mean ± SD)	3.7 ± 3.5	5.2 ± 3.8	3.6 ± 3.6	4.4 ± 3.7	4.8 ± 3.6	2.7 ± 3.0	2.7 ± 3.1	3.5 ± 3.3
Charlson score < 4	57.8%	36.8%	59.0%	47.9%	40.5%	71.7%	71.6%	61.0%
Charlson score ≥4	42.2%	63.2%	41.0%	52.1%	59.5%	28.4%	28.4%	39.0%
Frailty score (mean ± SD)	11.6 ± 7.6	15.3 ± 7.5	11.6 ± 7.0	13.5 ± 7.5	15.5 ± 7.2	8.1 ± 6.8	8.9 ± 6.9	11.0 ± 7.2
Frailty score 0–3 (well)	18.4%	9.3%	13.5%	12.4%	5.7%	34.2%	27.5%	18.4%
Frailty score 4–8	21.6%	12.3%	26.0%	19.3%	16.1%	25.2%	26.0%	23.5%
Frailty score 9–15 (pre-frail)	25.8%	22.1%	29.5%	23.0%	23.4%	20.6%	26.8%	27.9%
Frailty score ≥ 16 (frail)	34.2%	56.3%	31.1%	45.4%	54.8%	20.0%	19.7%	30.2%
Hypertension	65.2%	77.0%	65.7%	68.1%	73.3%	56.5%	56.7%	64.8%
Coronary artery disease	43.1%	57.3%	41.7%	50.9%	52.8%	32.2%	34.4%	41.1%

(Continues)

TABLE 2 (Continued)

		VKA (n = 2360)	Low-dose DOACs (n = 2520)			Standard-dose DOACs (n = 10 274)		
	Total (n = 15 154)	Warfarin (n = 2360)	Dabigatran 110 mg (n = 312)	Rivaroxaban 15 mg (n = 639)	Apixaban 2.5 mg (n = 1569)	Dabigatran 150 mg (n = 515)	Rivaroxaban 20 mg (n = 4188)	Apixaban 5 mg (n = 5571)
Acute myocardial infarction	9.1%	16.7%	6.1%	12.7%	13.5%	4.5%	5.4%	7.6%
Chronic heart failure	23.1%	40.4%	19.6%	27.1%	33.2%	13.6%	14.3%	20.3%
Cardiomyopathy	4.9%	7.2%	2.9%	4.4%	5.3%	4.5%	3.6%	5.0%
Other cardiac dysrhythmias	13.6%	16.8%	11.5%	12.1%	15.2%	9.7%	11.7%	13.8%
Valvular heart disease	10.6%	19.2%	8.7%	11.4%	13.9%	5.4%	6.4%	9.6%
Stroke/transient ischemic attack	12.5%	16.4%	16.0%	12.2%	15.9%	7.8%	8.6%	13.1%
Peripheral vascular (arterial) disease	16.9%	26.6%	13.5%	18.6%	20.9%	8.7%	12.2%	15.8%
Dyslipidemia	39.6%	50.2%	35.3%	41.2%	41.4%	30.5%	32.0%	41.2%
Diabetes	32.8%	42.3%	33.3%	34.0%	31.9%	30.9%	27.1%	33.3%
Major bleeding	19.3%	30.8%	19.2%	23.0%	27.7%	9.5%	12.6%	17.6%
Major intracranial bleeding	2.8%	3.6%	3.2%	2.2%	3.7%	1.6%	2.0%	3.0%
Major gastrointestinal bleeding	5.7%	8.0%	5.5%	6.7%	7.3%	4.1%	4.1% ç%	5.6%
Other sites of major bleeding	13.3%	23.6%	13.5%	16.9%	20.7%	4.3%	7.9%	11.3%
Chronic kidney disease	25.3%	51.6%	17.0%	38.0%	44.9%	10.1%	10.9%	19.9%
Chronic kidney disease ≤30 ml/min	3.8%	14.0%	1.3%	3.0%	5.4%	0.6%	1.0%	1.6%
Acute renal failure	16.0%	34.8%	9.0%	21.3%	27.1%	6.0%	6.5%	12.8%
Liver disease	2.0%	2.8%	2.9%	1.6%	2.0%	3.3%	1.4%	2.0%
COPD/asthma	28.2%	35.5%	23.4%	30.5%	32.6%	26.6%	25.2%	26.4%
Helicobacter pylori infection	0.5%	0.6%	0.3%	1.6%	0.3%	0.4%	0.3%	0.5%
Depression	6.8%	8.4%	5.5%	7.2%	8.2%	6.0%	5.8%	6.6%

TABLE 2 (Continued)

	Total (n = 15 154)	VKA (n = 2360)	Low-dose DOACs (n = 2520)			Standard-dose DOACs (n = 10 274)		
		Warfarin (n = 2360)	Dabigatran 110 mg (n = 312)	Rivaroxaban 15 mg (n = 639)	Apixaban 2.5 mg (n = 1569)	Dabigatran 150 mg (n = 515)	Rivaroxaban 20 mg (n = 4188)	Apixaban 5 mg (n = 5571)
Medical procedures								
Cardiac catheterization	3.5%	4.8%	2.6%	3.6%	2.9%	3.7%	2.6%	3.8%
Percutaneous coronary surgery—stent	2.5%	4.2%	2.6%	3.6%	2.7%	1.9%	1.8%	2.2%
Coronary artery bypass graft	0.8%	1.1%	0.0%	0.8%	0.3%	0.6%	0.6%	1.1%
For cerebrovascular disease	0.9%	1.4%	0.7%	0.5%	0.6%	0.0%	1.0%	0.9%

Abbreviations: COPD, chronic obstructive pulmonary disease; DOACs, direct oral anticoagulants; n, number of patients; OACs, oral anticoagulants; Q_1, first quartile; Q_3, third quartile; SD, standard deviation; VKA, vitamin K antagonist.

The proportion of patients starting on a low-dose DOAC was higher among women than among men. Compared with warfarin, the year of initiation was one of the main factors associated with DOAC initiation for both sexes. Women starting to take a DOAC were older and more likely to have a $CHADS_2$ score ≥ 2 than men starting to take a DOAC relative to warfarin. The choice of a low-dose DOAC versus a standard-dose DOAC was mainly driven by age and CKD status, and a higher $CHADS_2$ score for both sexes.

Increased prescription of DOACs to patients with AF is in line with the guidelines that recommend DOAC (rather than warfarin) when OAC therapy is indicated.[3,4,33–37] For instance, on one side, guidelines recommendations were initially based on the results of several large randomized clinical trials, showing that (i) DOACs are non-inferior or superior to warfarin in reducing the risk of AF-associated stroke or systemic embolism, and (ii) the risk of major bleeding is lower for DOACs than for warfarin or is at least similar.[38–40] But, on the other side, data published from other sources of data than randomized clinical trials and of other different populations may be related to the observed changes in prescription and were influenced by apixaban's safety profile based on post hoc analysis and network meta-analysis,[41,42] and the Food and Drug Administration warned of a significant risk of bleeding and acute myocardial infarction,[43,44] and the suggested net clinical benefit of DOACs versus warfarin in women based on meta-analysis.[45] Physicians might be reluctant to prescribe dabigatran in patients with impaired renal function, older patients, patients with morbidities, and patients with another preference. Our findings are in line with another report in which the increase in DOAC prescriptions among incident OAC users with non-valvular AF was predominantly driven by apixaban.[46] Among DOAC users, the odds of apixaban prescription increased with age, women sex, stroke risk, bleeding risk, and comorbidities. In both sexes, patients starting on warfarin had a higher comorbidity burden.[46]

In the present study, several determinants were independently associated with DOAC initiation (relative to warfarin initiation). In both sexes, one of the major determinants of low-dose and standard-dose DOACs initiation versus warfarin was the year of initiation. This was followed by older age, which determined the use of all low-dose DOACs among both sexes. In women only, those with a higher $CHADS_2$ score were more likely to receive a low dose of dabigatran and rivaroxaban versus warfarin. We speculate that the impact of the year of initiation is mainly driven to clinical experience since the approval of DOACs for AF in Canada began in October 2010 with dabigatran, followed by rivaroxaban in January 2012 and apixaban in December 2012. But, the reimbursement of DOACs by the RAMQ began in April 2011 for dabigatran, followed by rivaroxaban in October 2012 and apixaban in October 2013, which represent overall more than 1 year after the approval of RAMQ reimbursement.

The choice of initiating a low-dose DOAC versus a standard-dose DOAC was mainly driven by older age (80 and over) for all DOACs and both sexes, as expected from the guidelines. Women and men with a higher $CHADS_2$ score were more likely to receive a low dose of dabigatran and rivaroxaban versus their respective standard dose.

TABLE 3 Factors associated with the initiation of DOACs (vs. warfarin) in women, by the type of DOACs and the dose

Factors	Low-dose dabigatran (ref: warfarin) Adjusted OR (95% CI)	Low-dose rivaroxaban (ref: warfarin) Adjusted OR (95% CI)	Low-dose apixaban (ref: warfarin) Adjusted OR (95% CI)	Standard-dose dabigatran (ref: warfarin) Adjusted OR (95% CI)	Standard-dose rivaroxaban (ref: warfarin) Adjusted OR (95% CI)	Standard-dose apixaban (ref: warfarin) Adjusted OR (95% CI)
Year of initiation						
2014	Reference	Reference	Reference	Reference	Reference	Reference
2015	0.84 (0.62–1.14)	**1.40 (1.16–1.69)**	**2.29 (1.98–2.64)**	**1.53 (1.09–2.14)**	**1.74 (1.49–2.03)**	**2.36 (2.06–2.71)**
2016	**1.53 (1.13–2.07)**	**1.82 (1.48–2.25)**	**4.03 (3.45–4.70)**	**2.57 (1.81–3.65)**	**2.84 (2.40–3.37)**	**5.39 (4.65–6.25)**
2017	**2.78 (2.03–3.80)**	**2.59 (2.06–3.26)**	**4.77 (4.00–5.68)**	**3.35 (2.28–4.91)**	**4.10 (3.38–4.97)**	**8.36 (7.09–9.86)**
Age (years)						
<65	Reference	Reference	Reference	Reference	Reference	Reference
65–79	**2.47 (1.20–5.07)**	**5.69 (2.83–11.43)**	**3.47 (2.01–6.01)**	1.14 (0.77–1.68)	1.10 (0.87–1.40)	**1.84 (1.45–2.34)**
≥80	**2.96 (1.45–6.07)**	**7.94 (3.96–15.92)**	**17.91 (10.45–30.71)**	**0.08 (0.05–0.15)**	**0.29 (0.22–0.37)**	**0.59 (0.46–0.75)**
$CHADS_2$ score (≥2 vs. <2)	**1.69 (1.23–2.32)**	**1.26 (1.01–1.58)**	1.11 (0.93–1.33)	**0.61 (0.44–0.84)**	0.91 (0.77–1.07)	1.10 (0.95–1.28)
HAS-BLED score (≥3 vs. <3)	**0.54 (0.39–0.75)**	**0.77 (0.62–0.95)**	**0.76 (0.65–0.89)**	**0.63 (0.43–0.92)**	**0.64 (0.54–0.76)**	**0.77 (0.66–0.89)**
Frailty score (≥9 vs. <9)	**0.55 (0.41–0.73)**	0.83 (0.68–1.03)	0.97 (0.82–1.15)	**0.61 (0.44–0.84)**	**0.59 (0.50–0.69)**	**0.77 (0.66–0.90)**
CAD, including AMI (yes vs. no)	**0.76 (0.58–0.99)**	**0.81 (0.68–0.96)**	0.89 (0.78–1.00)	0.84 (0.61–1.14)	**0.75 (0.65–0.86)**	**0.75 (0.66–0.84)**
Stroke/transient ischemic attack (yes vs. no)	0.95 (0.67–1.35)	**0.72 (0.57–0.92)**	0.88 (0.75–1.04)	**1.72 (1.13–2.61)**	**0.79 (0.65–0.97)**	0.96 (0.82–1.12)
Major bleeding (yes vs. no)	1.10 (0.79–1.52)	0.88 (0.71–1.07)	0.92 (0.79–1.06)	**0.60 (0.40–0.90)**	**0.66 (0.55–0.79)**	**0.72 (0.62–0.83)**
Antiplatelet agent (yes vs. no)	0.95 (0.74–1.21)	1.04 (0.88–1.22)	0.98 (0.87–1.11)	1.21 (0.91–1.61)	0.99 (0.87–1.14)	1.00 (0.89–1.13)
CKD (<60 and ≥30 ml/min vs. ≥60 ml/min)	**0.43 (0.33–0.56)**	**0.47 (0.40–0.56)**	**0.52 (0.46–0.59)**	**0.47 (0.34–0.66)**	**0.34 (0.29–0.39)**	**0.46 (0.41–0.51)**
CKD (<30 ml/min vs. ≥60 ml/min)	**0.09 (0.03–0.25)**	**0.12 (0.07–0.21)**	**0.20 (0.15–0.26)**	*n* too small	**0.03 (0.01–0.05)**	**0.10 (0.08–0.14)**

Note: The results are quoted as adjusted odds ratios.

Bold values indicate statistical significance.

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DOACs, direct oral anticoagulants; *n*, number of patients; OR, odds ratio; ref, reference.

TABLE 4 Factors associated with the initiation of DOACs (vs. warfarin) in men, by the type of DOACs and the dose

Factors	Low-dose dabigatran (ref: warfarin) Adjusted OR (95% CI)	Low-dose rivaroxaban (ref: warfarin) Adjusted OR (95% CI)	Low-dose apixaban (ref: warfarin) Adjusted OR (95% CI)	Standard-dose dabigatran (ref: warfarin) Adjusted OR (95% CI)	Standard-dose rivaroxaban (ref: warfarin) Adjusted OR (95% CI)	Standard-dose apixaban (ref: warfarin) Adjusted OR (95% CI)
Year of initiation						
2014	Reference	Reference	Reference	Reference	Reference	Reference
2015	1.04 (0.74–1.44)	1.25 (0.99–1.57)	**2.04 (1.69–2.46)**	1.22 (0.90–1.65)	**1.92 (1.64–2.24)**	**2.25 (1.95–2.60)**
2016	**1.78 (1.27–2.50)**	**1.52 (1.17–1.97)**	**3.16 (2.60–3.86)**	**3.13 (2.30–4.25)**	**3.03 (2.56–3.60)**	**4.67 (4.01–5.45)**
2017	**2.61 (1.81–3.76)**	**2.70 (2.06–3.54)**	**4.12 (3.30–5.15)**	**3.09 (2.21–4.32)**	**3.75 (3.09–4.54)**	**7.04 (5.92–8.36)**
Age (years)						
<65	Reference	Reference	Reference	Reference	Reference	Reference
65–79	**3.16 (1.49–6.73)**	**2.58 (1.53–4.35)**	**3.01 (1.77–5.12)**	1.08 (0.79–1.49)	0.93 (0.75–1.15)	**1.40 (1.13–1.73)**
≥80	**6.70 (3.14–14.27)**	**4.90 (2.90–8.28)**	**13.77 (8.15–23.26)**	**0.11 (0.07–0.18)**	**0.30 (0.24–0.37)**	**0.61 (0.49–0.76)**
$CHADS_2$ score (≥2 vs. <2)	1.12 (0.80–1.56)	0.98 (0.76–1.26)	1.15 (0.93–1.44)	**0.71 (0.54–0.93)**	**0.71 (0.60–0.83)**	0.92 (0.79–1.06)
HAS-BLED score (≥3 vs. <3)	**0.54 (0.38–0.78)**	**0.72 (0.56–0.94)**	**0.69 (0.56–0.85)**	**0.54 (0.38–0.76)**	**0.61 (0.51–0.73)**	**0.81 (0.70–0.95)**
Frailty score (≥9 vs. <9)	**0.70 (0.50–0.97)**	**0.70 (0.54–0.91)**	0.90 (0.72–1.12)	**0.59 (0.44–0.79)**	**0.77 (0.66–0.91)**	**0.77 (0.66–0.90)**
CAD, including AMI (yes vs. no)	0.92 (0.69–1.23)	1.13 (0.92–1.40)	0.97 (0.82–1.14)	0.98 (0.75–1.30)	**0.84 (0.73–0.97)**	**0.87 (0.77–0.99)**
Stroke/transient ischemic attack (yes vs. no)	1.30 (0.90–1.88)	0.85 (0.64–1.13)	1.05 (0.86–1.28)	0.94 (0.62–1.43)	0.88 (0.72–1.06)	0.98 (0.83–1.16)
Major bleeding (yes vs. no)	1.00 (0.70–1.44)	0.95 (0.74–1.21)	1.00 (0.84–1.20)	0.70 (0.48–1.03)	**0.84 (0.71–0.99)**	**0.78 (0.68–0.91)**
Antiplatelet agent (yes vs. no)	1.03 (0.78–1.35)	0.94 (0.74–1.14)	1.01 (0.87–1.18)	**0.76 (0.59–0.97)**	0.88 (0.77–1.00)	0.91 (0.80–1.02)
CKD (<60 and ≥30 ml/min vs. ≥60 ml/min)	**0.39 (0.29–0.54)**	**0.75 (0.61–0.93)**	**0.77 (0.65–0.92)**	**0.54 (0.40–0.73)**	**0.36 (0.31–0.41)**	**0.47 (0.41–0.53)**
CKD (<30 ml/min vs. ≥60 ml/min)	**0.06 (0.02–0.17)**	**0.17 (0.10–0.28)**	**0.31 (0.23–0.42)**	**0.04 (0.01–0.13)**	**0.05 (0.04–0.08)**	**0.07 (0.05–0.09)**

Note: The results are quoted as adjusted odds ratios.

Bold values indicate statistical significance.

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DOACs, direct oral anticoagulants; OR, odds ratio; ref, reference.

TABLE 5 Factors associated with the initiation of low-dose DOACs (vs. standard-dose) in women and men, by the type of DOACs

	Women			Men		
Factors	**Low-dose dabigatran (ref: standard dose) adjusted OR (95% CI)**	**Low-dose rivaroxaban (ref: standard dose) adjusted OR (95% CI)**	**Low-dose apixaban (ref: standard dose) adjusted OR (95% CI)**	**Low-dose dabigatran (ref: standard dose) adjusted OR (95% CI)**	**Low-dose rivaroxaban (ref: standard dose) adjusted OR (95% CI)**	**Low-dose apixaban (ref: standard dose) adjusted OR (95% CI)**
Year of initiation						
2014	Reference	Reference	Reference	Reference	Reference	Reference
2015	**0.50 (0.30–0.84)**	0.83 (0.67–1.02)	0.92 (0.78–1.09)	0.98 (0.58–1.65)	**0.64 (0.50–0.83)**	0.87 (0.71–1.06)
2016	**0.56 (0.34–0.94)**	**0.61 (0.49–0.76)**	**0.66 (0.57–0.78)**	0.75 (0.45–1.24)	**0.50 (0.38–0.65)**	**0.66 (0.55–0.81)**
2017	**0.58 (0.34–0.99)**	**0.63 (0.50–0.79)**	**0.52 (0.44–0.61)**	0.70 (0.41–1.20)	**0.64 (0.49–0.84)**	**0.49 (0.40–0.60)**
Age (years)						
<65	Reference	Reference	Reference	Reference	Reference	Reference
65–79	2.01 (0.92–4.38)	**4.99 (2.53–9.83)**	**1.97 (1.17–3.31)**	**2.79 (1.28–6.08)**	**2.65 (1.61–4.35)**	**2.03 (1.22–3.38)**
≥80	**33.98 (14.38–80.29)**	**29.23 (14.84–57.61)**	**35.12 (21.02–58.67)**	**59.12 (25.44–137.41)**	**16.90 (10.25–27.88)**	**22.71 (13.75–37.52)**
$CHADS_2$ score (≥2 vs. <2)	**3.15 (2.01–4.92)**	**1.28 (1.04–1.58)**	**0.86 (0.73–0.99)**	**2.04 (1.32–3.15)**	**1.32 (1.04–1.68)**	1.19 (0.98–1.43)
HAS-BLED score (≥3 vs. <3)	0.83 (0.47–1.48)	1.21 (0.96–1.52)	1.03 (0.89–1.20)	0.97 (0.56–1.68)	1.23 (0.94–1.60)	0.88 (0.73–1.06)
Frailty score (≥9 vs. <9)	0.76 (0.47–1.21)	**1.44 (1.18–1.76)**	**1.23 (1.07–1.42)**	1.25 (0.78–2.00)	0.95 (0.74–1.21)	1.18 (0.98–1.43)
CAD, including AMI (yes vs. no)	0.94 (0.50–1.50)	1.13 (0.94–1.36)	**1.17 (1.04–1.32)**	0.87 (0.56–1.38)	**1.26 (1.02–1.55)**	1.12 (0.97–1.30)
Stroke/transient ischemic attack (yes vs. no)	**0.50 (0.26–0.95)**	0.87 (0.67–1.15)	0.93 (0.79–1.09)	1.48 (0.81–2.70)	0.94 (0.69–1.28)	1.02 (0.84–1.23)
Major bleeding (yes vs. no)	1.45 (0.80–2.64)	**1.30 (1.02–1.65)**	**1.28 (1.10–1.48)**	1.17 (0.64–2.13)	1.15 (0.88–1.50)	**1.32 (1.11–1.57)**
Antiplatelet agent (yes vs. no)	1.12 (0.77–1.73)	1.07 (0.90–1.28)	0.99 (0.88–1.11)	1.38 (0.91–2.10)	1.10 (0.90–1.34)	1.09 (0.94–1.26)
CKD (<60 and ≥30 ml/min vs. ≥60 ml/min)	1.31 (0.79–2.16)	**1.69 (1.40–2.04)**	**1.23 (1.09–1.38)**	1.46 (0.89–2.38)	**2.62 (2.11–3.24)**	**2.00 (1.72–2.32)**
CKD (<30 ml/min vs. ≥60 ml/min)	*n* too small	**6.84 (2.72–17.16)**	**3.05 (2.01–4.63)**	4.08 (0.76–21.84)	**4.29 (2.27–8.12)**	**7.22 (4.94–10.54)**

Note: The results are quoted as adjusted odds ratios.

Bold values indicate statistical significance.

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DOACs, direct oral anticoagulants; *n*, number of patients; OR, odds ratio; ref, reference.

However, women with a higher frailty score, prior major bleeding, and CKD status were more likely to initiate a low dose of rivaroxaban and apixaban than standard dose of rivaroxaban and apixaban. Among men, the factors associated with initiation of low dose of rivaroxaban and apixaban versus standard-dose of rivaroxaban and apixaban were CKD status and prior major bleeding for only apixaban. Physicians should be concerned about the prevalence of low-dose DOAC use in clinical practice and the factors related to this use in heterogenous populations, giving that data on the effectiveness and safety of low-dose DOACs are still limited.[13–15]

Consistently described sex differences in the epidemiology, pathophysiology, clinical presentation, and prognosis of AF may influence the effectiveness of AF treatment. Taking account of these sex differences provides an opportunity to improve outcomes in women with AF.[47–53] For instance, a twice-daily dose of apixaban 5 mg should be lowered to 2.5 mg twice-daily when at least two of the three criteria (age ≥ 80, creatinine ≥1.5 mg/dl, and body weight ≤ 60 kg) are met. As mentioned in the introduction, a recent systematic review of observational studies reported that close to 50% of patients receiving a low dose of apixaban do not meet at least two of the three criteria.[15] In this systematic review of observational studies versus randomized clinical trials, the higher risk profiles of AF patients in clinical practice treated with apixaban 2.5 mg (vs. 5 mg) may explain (i) the higher-than-expected thromboembolic event rates in the clinic and (ii) the higher rates of major bleeding and mortality.[15] In addition, some recent research studies reported the sex differences in the management of OAC and outcomes[12,54] but further research investigating sex-specific differences in the appropriateness of DOACs prescription in different populations of clinical practice is still needed. There is also a need of a well-designed randomized clinical trial that compares each DOAC and specific dose with regard to sex-specific of efficacy and safety in a representative population of clinical practice.

Our study had several strengths. First, it was the first study to have investigated sex differences in OAC initiation and to have stratified the analyses by the DOAC dose (low vs. standard). Second, we used a large, well-characterized, population-based cohort, which enabled us to evaluate many different factors. Third, our factors were well defined and had been validated in previous studies. However, our study also had some limitations. First, its findings were derived from administrative databases and did not contain information on clinical factors, such as the body mass index or the exact creatinine clearance rate but we have developed and validated algorithms able to determine the categories of eGFR, that is, ≥60, between ≥30 and 60 and <30 ml/min. Second, our results in a population of mostly Caucasians might not be generalizable to other patient populations and other ethnic groups. Third, and although we included a variety of relevant confounders in our analysis, we cannot rule out the possibility that unobserved factors (such as physician and patient preferences) might be associated with the selection of an OAC. Fourth, the claims databases do not include information on the use of over-the-counter medications like acetylsalicylic acid, where the over-the-counter use is very low in older adults. Nevertheless, we would expect any underestimation to be similar in all study groups. Lastly, and given that our data source did not contain data on the body weight and the exact creatinine clearance rate, the appropriateness of dose reduction in DOAC users cannot be assessed. Further studies are required to assess sex differences in the appropriateness of DOAC dose reduction and to identify factors of inappropriate dose reduction.

OAC initiation patterns were broadly similar in men and women. Our most important finding was that women were more likely than men to received low-dose DOACs. The most notable factors independently associated with low-dose DOAC initiation were older age (in both sexes) and a high $CHADS_2$ score (in women only) relative to warfarin. Further research should investigate (i) sex-specific differences in appropriateness of DOAC prescription, (ii) patterns of OAC use in different populations and subgroups in clinical practice, and (iii) the comparative effectiveness and safety of various OACs and doses.

AUTHORS' CONTRIBUTIONS

AL contributed to part of the conceptualization of the study design, ran a part of the analyses and wrote the article. MD provided programming guidance and final data analysis. SP provide the conceptual framework for the study design, access to data, revisions and final approval of the published article. All authors aided in interpreting the results, worked on the manuscript, and approved the final.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest. Author Marc Dorais was employed by StatSciences Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly or made available to reviewers, because of privacy/ethical restrictions on account of provincial "Commission d'accès à l'information du Gouvernement du Québec" law.

ETHICS STATEMENT

The study was approved by an institutional review board of University of Montreal, Montreal, Quebec, Canada (Project Number: 2017-1132).

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