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ORIGINAL ARTICLE

# Trends in oral anticoagulant use in patients with atrial fibrillation in Belgium from 2013 to 2019: A nationwide cohort study

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**Aim:** Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly preferred over vitamin K antagonists (VKAs) in atrial fibrillation (AF) management. However, differences in oral anticoagulant (OAC) prescribing according to patient's age, sex and physician's specialty may be present. Therefore, incident and prevalent use of OACs, NOACs and VKAs, stratified by age, sex and prescriber, and factors associated with the choice of OAC were investigated.

**Methods:** Using two Belgian nationwide healthcare databases, AF patients ≥45 years old with ≥1 OAC prescription claim between 2013 and 2019 were identified. OAC use was investigated per half-year. Factors influencing NOAC *vs*. VKA initiation were identified by multivariable logistic regression.

**Results:** Among 448 661 included OAC-treated AF patients, 297 818 were newly treated. Incident OAC use ranged from 45–49 to 42–44 users/10 000 persons between 2013 and 2019, whereas prevalent OAC use increased from 337 to 435 users/10 000 persons. Incident and prevalent NOAC use exceeded VKA use since 2013 and 2015, respectively, and NOACs represented 92% of incident and 81% of prevalent OAC users in 2019. Apixaban was the most frequently used NOAC since 2016. NOACs were significantly more prescribed by cardiologists and to older patients, whereas VKAs were more initiated in patients with cardiovascular, renal and hepatic comorbidities. Prevalent OAC use increased less in women than men (25.3% *vs*. 33.0% between 2013 and 2019) and female subjects had 5% significantly lower odds of NOAC *vs*. VKA initiation than men.

**Conclusion:** Since 2013, prevalent anticoagulant use increased almost one third in Belgium, while incident use was stable. Potential (N)OAC underuse in women requires further exploration.

**Principal Investigator statement** The authors confirm that the principal investigators for this paper are Lies Lahousse and Maxim Grymonprez. No patients were directly involved.

KEYWORDS
anticoagulant, atrial fibrillation, nationwide cohort study, NOAC, pharmacoepidemiology, VKA

## 1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide.[1,2] Due to the associated thromboembolic risk, oral anticoagulants (OAC) are essential in AF management.[3] Vitamin K antagonists (VKAs) were the first choice anticoagulant for decades but were often underused due to their narrow therapeutic window requiring routine coagulation monitoring, slow onset of action and multiple drug and food interactions.[3,4] Since 2010, non-vitamin K antagonist oral anticoagulants (NOACs) have emerged as effective and safe alternatives to VKAs, thanks to their fast onset of action, fixed dosing regimen without the need for monitoring, fewer interactions and lower intracranial bleeding risk.[3] In Belgium, **dabigatran** was the first approved NOAC for stroke prevention in AF since August 2012, followed by **rivaroxaban** (September 2012), **apixaban** (September 2013) and **edoxaban** (October 2016).[5,6] Following their approval, AF-related anticoagulant use has almost doubled worldwide in the last decade.[7] Since 2014, NOACs have been preferred over VKAs in incident users worldwide, and since 2017, prevalent NOAC users have surpassed VKA users.[7] However, which patient characteristics have influenced the choice of NOAC over VKA in newly diagnosed AF patients, and whether these differ between primary and secondary care physicians, are less established.

As AF incidence increases with age and AF is more common in men, anticoagulants tend to be more frequently used among older than younger and male than female AF patients.[2,3,8–11] Since the 2010 European Society of Cardiology (ESC) AF guidelines, the $CHA_2DS_2$-VASc instead of $CHADS_2$ score is recommended to assess a patient's thromboembolic risk.[7,12] Given the additional inclusion of being 65–74 years old and female sex as thromboembolic risk factors, it is unclear whether the age and sex gap in anticoagulant prescribing has minimized in recent years.

Therefore, we aimed to investigate temporal trends in incident and prevalent use of OACs, NOACs and VKAs in Belgian AF patients on a full-population scale from 2013 to 2019, stratified according to age, sex and prescriber type. Moreover, factors associated with the choice of OAC in newly treated AF patients were explored.

### What is already known about this subject

- Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly preferred over vitamin K antagonists (VKAs) in atrial fibrillation (AF) management.
- Following their approval, the proportion of anticoagulant use in AF patients worldwide has almost doubled, although which patient and prescriber characteristics have influenced the choice of anticoagulant are less well established.

### What this study adds

- Prevalent anticoagulant use in Belgium increased one third between 2013 and 2019, while incident use remained stable.
- NOACs were more prescribed by cardiologists and to older AF patients, whereas VKAs were more initiated in patients with cardiovascular, renal and hepatic comorbidities.
- However, anticoagulant use in female patients <75 years old followed in primary care was lagging.

## 2 | METHODS

### 2.1 | Source population

Two nationwide databases, the InterMutualistic Agency (IMA) database and Minimal Hospital Dataset (MHD), provided the source population. The IMA centralizes all claims data from Belgian health insurance funds on reimbursed ambulatory and hospital care, including demographic characteristics (e.g., sex and age), medical procedures (diagnostic or therapeutic procedures and other reimbursed care) and medication prescription claims (e.g., dispensing date, Anatomical Therapeutic Chemical Classification [ATC] code, dose strength, number of pills and packages supplied and prescriber type).[13–15] Since health insurance is legally mandatory in Belgium, the source population represents all legal residents with reimbursed medication or care. The MHD, collected by the Belgian Ministry of Health, aggregates hospital discharge diagnoses of every admission in Belgian hospitals (including hospitalizations, day-care stays and emergency room contacts), coded in International Classification of Diseases (ICD) codes (ICD-9 up to 2014, ICD-10 from 2015 onwards).[13,15,16] All single cases of the study population could be identified in both databases. The trusted third party 'eHealth' was responsible for deterministically linking both databases using the national social security number as unique patient identifier. After applying an encrypting procedure for privacy protection, only pseudonymized data were available to the researchers on the secured IMA servers.

This study was approved by the IMA and MHD database administrators and by the 'Sectoral Committee of Social Security and Health, Section Health', a subcommittee of the Belgian Commission for the Protection of Privacy (approval code IVC/KSZG/20/344).[17]

## 2.2 | Study population

Subjects ≥45 years old with ≥1 year coverage by a Belgian health insurance fund on the first date of filling an OAC prescription (=index date) during the study period from 1 January 2013 to 31 December 2019 were included in the study (Figure S1). VKA (**warfarin**, **acenocoumarol** and **phenprocoumon**) and NOAC users (dabigatran, rivaroxaban, apixaban and edoxaban) were included.

In order to specifically include non-valvular AF patients and avoid competing treatment indications, subjects were excluded in case of total hip or knee replacement surgery, or diagnosis of deep vein thrombosis or pulmonary embolism ≤6 months before the index date, based on specific ICD and/or medical procedure codes (Table S1). Moreover, in order to investigate AF patients eligible for VKAs and NOACs, subjects with valvular AF (mechanical prosthetic heart valve or moderate/severe mitral stenosis) or end-stage renal disease (chronic kidney disease [CKD] stage V and/or dialysis) were excluded. Lastly, subjects with ≥2 prescription claims of different types or doses of oral anticoagulants on the index date, or subjects treated with NOAC doses not approved for stroke prevention in AF (e.g., rivaroxaban 10 mg) were excluded. However, given that temporal trends in anticoagulant use were investigated in AF patients treated in ambulatory and hospital care, the study population was not restricted to recently hospitalized AF patients with an ICD-coded hospital discharge diagnosis of AF.[18] Nevertheless, as a sensitivity analysis, only subjects with an ICD-coded diagnosis of AF ≤1 year before or ≤90 days after the index date (to account for diagnostic lag) were investigated to increase the likelihood of treatment indication.[18,19]

## 2.3 | Trends in anticoagulant use

A repeated cross-sectional design was used to calculate incident and prevalent OAC use by class (e.g., NOAC) and type (e.g., dabigatran) for each half-year of the study period, based on medication prescription claims. Subjects were considered as OAC-experienced if an OAC prescription was filled ≤1 year before the index date. Incident use was defined as the first OAC use during the study period in OAC-naïve AF patients to ensure that subjects were an incident user only once. Prevalent OAC use was defined as ≥1 OAC dispensing during a specific half-year. If a subject used several OAC types after the index date during one half-year period, the most frequently dispensed OAC was considered dominant for that half-year for the calculation of prevalent OAC use by class and type, in order to avoid multiple inclusion of the same subject in one half-year. Follow-up ended in case of death, emigration or end of the study period.

## 2.4 | Covariates

Baseline characteristics were assessed of OAC-naïve AF patients, including age, sex, comorbidities, comedication and prescriber type. Comorbidities were identified using ICD-coded diagnoses (e.g., cancer), medical procedure codes (e.g., cancer-related surgery) and/or ATC-coded prescription claims (e.g., antineoplastic drugs) ≤1 year before the index date (Table S1).[8,10,20,21] Comorbidities included hypertension, coronary and peripheral artery disease (CAD/PAD), heart failure, valvular heart disease, dyslipidaemia, CKD, chronic liver disease, chronic lung disease (COPD, asthma, etc.), obstructive sleep apnoea, cancer, upper and lower gastrointestinal tract disorders (gastroesophageal reflux disease or peptic ulcer disease and diverticulosis, angiodysplasia, colorectal polyposis or haemorrhoids, respectively), diabetes mellitus, thyroid disease, anaemia, osteoporosis, dementia, Parkinson's disease, history of falling, frailty (using a claims-based frailty indicator[22]), prior thromboembolism (stroke or systemic embolism) and prior major or clinically relevant non-major bleeding (intracranial, gastrointestinal, urogenital or other bleeding event necessitating hospitalization). Missing ICD data (due to the transition from ICD-9 to ICD-10 in 2015 and incomplete data transfer in 2019) were imputed through multiple imputation by chained equations.

Comedication use was identified with ATC-coded prescription claims ≤6 months before the index date. Cardiovascular and potential bleeding-related drugs (antiplatelets [**aspirin** and/or P2Y12 inhibitors], non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin and serotonin and norepinephrine reuptake inhibitors [SSRI/SNRI] and corticosteroids) were considered.

Prescriber type of the physician initiating the OAC was assessed using the last three digits of the physician's identification code of the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI) and categorized as primary care physician, cardiologist or other secondary care physician.

Lastly, the $CHA_2DS_2$-VASc score, HAS-BLED score and age-adjusted Charlson Comorbidity Index (CCI) were calculated.[1,23] Due to missing laboratory values, a modified HAS-BLED score was used without 'labile INR'.[8,24] Alcohol abuse was identified with ICD (e.g., alcoholic liver disease), ATC (e.g., **disulfiram**) and medical procedure codes (e.g., visit to psychologist for alcohol abuse), as no data on alcohol consumption were available.

## 2.5 | Statistical analyses

Mean ± standard deviation, and counts and percentages were presented for continuous and categorical variables, respectively. Incident use was calculated by dividing the number of first OAC users in each half-year by the number of OAC-naïve Belgian inhabitants ≥45 years old in the IMA database at the start of the half-year (1 January and 1 July). Prevalent use was calculated by dividing the total number of OAC users in each half-year by the number of Belgian inhabitants ≥45 years old at the start of the half-year. Results were visually presented in time series plots and stratified by age, sex and prescriber type.

Multivariable logistic regression was performed to identify factors associated with the choice for NOACs *vs.* VKAs in incident users. Age (≥75 *vs.* <75 years), sex, cardiovascular comorbidities, geriatric traits (e.g., frailty), thromboembolism- and/or bleeding-related comorbidities (e.g., cancer), bleeding-related drugs, prescriber type and time period (dichotomized as July 2016–December 2019 *vs.* January 2013–June 2016) were fitted in a multivariable model with backward elimination. Only statistically significant factors using a two-sided *P* value of <.05 were retained in the final model. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Results were visualized in forest plots and stratified by age, sex, time period and prescriber type. Analyses were performed in R (R version 3.6.0).

## 2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[25]

# 3 | RESULTS

## 3.1 | Baseline characteristics

From 2013 to 2019, 448 661 OAC-treated AF subjects were included (prevalent users), namely, 260 184 NOAC and 188 477 VKA users. Among these, 297 818 were incident OAC users, namely, 232 739 NOAC and 65 079 VKA users (Figure 1). Table 1 illustrates the baseline characteristics of incident OAC users. Incident NOAC and VKA users were on average 76.2 ± 10.3 and 70.9 ± 12.1 years old, and 47.6% and 46.7% were female, respectively. Among incident NOAC and VKA users, 4.8% and 12.9% were at low thromboembolic risk ($CHA_2DS_2$-VASc score 0 in men, 1 in women), 11.3% and 15.6% were at intermediate risk (score 1 in men, 2 in women), and 83.9% and 71.6% were at high risk (score ≥2 in men, ≥3 in women), respectively.

## 3.2 | Incident use

Incident OAC use ranged from 45–49 users in 2013 to 42–44 users per 10 000 OAC-naïve persons ≥45 years old in 2019 (Figure 2A).

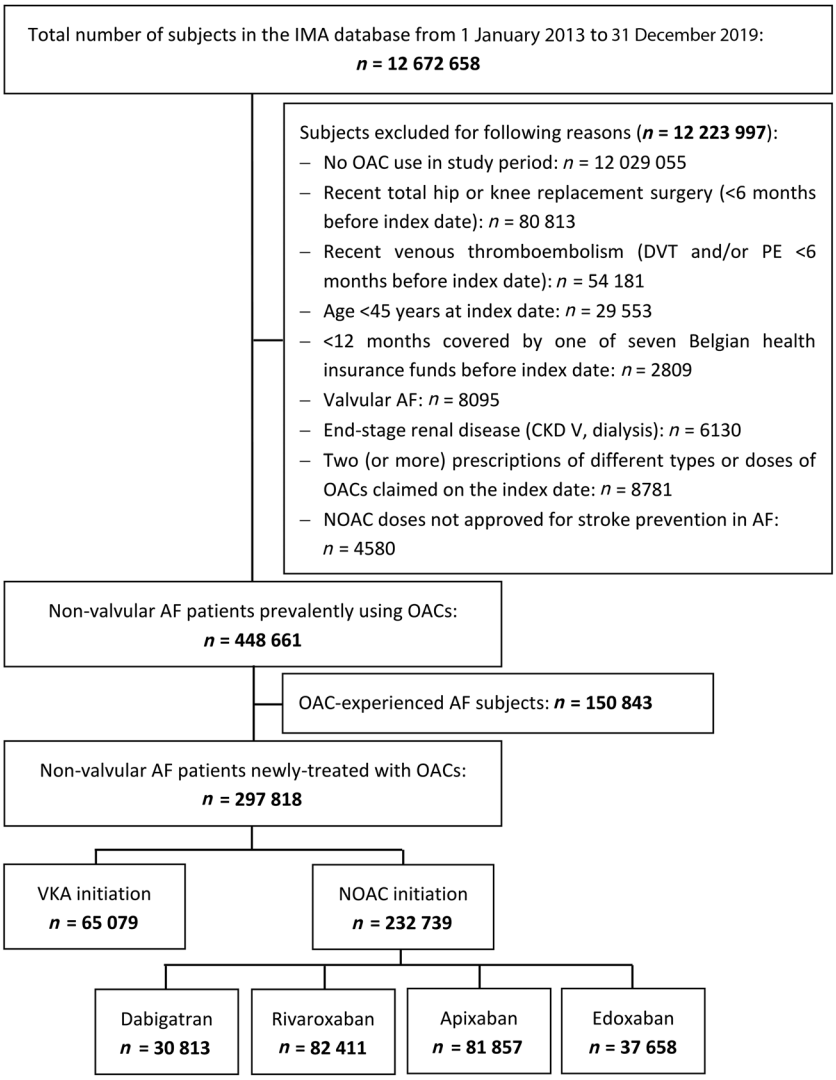


**FIGURE 1** Flowchart of study population. AF, atrial fibrillation; CKD, chronic kidney disease; DVT, deep vein thrombosis; IMA, InterMutualistic Agency; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist

**TABLE 1** Baseline characteristics of OAC-naïve AF subjects (incident users)

| Patient characteristics | VKA ($n = 65\,079$) | NOAC | | | | |
|---|---|---|---|---|---|---|
| | | Overall ($n = 232\,739$) | Dabigatran ($n = 30\,813$) | Rivaroxaban ($n = 82\,411$) | Apixaban ($n = 81\,857$) | Edoxaban ($n = 37\,658$) |
| Age (years) | 70.9 ± 12.1 | 76.2 ± 10.3 | 75.8 ± 9.9 | 75.4 ± 10.5 | 77.3 ± 9.9 | 75.9 ± 10.5 |
| <65 years | 22 512 (34.6%) | 31 136 (13.4%) | 4125 (13.4%) | 12 668 (15.4%) | 8823 (10.8%) | 5520 (14.7%) |
| 65–74 years | 16 157 (24.8%) | 66 950 (28.8%) | 9168 (29.8%) | 24 101 (29.2%) | 22 444 (27.4%) | 11 237 (29.8%) |
| 75–84 years | 17 645 (27.1%) | 85 594 (36.8%) | 11 763 (38.2%) | 30 127 (36.6%) | 30 769 (37.6%) | 12 935 (34.3%) |
| ≥85 years | 8765 (13.5%) | 49 059 (21.1%) | 5757 (18.7%) | 15 515 (18.8%) | 19 821 (24.2%) | 7966 (21.2%) |
| Female | 30 412 (46.7%) | 110 737 (47.6%) | 14 334 (46.5%) | 38 781 (47.1%) | 40 201 (49.1%) | 17 421 (46.3%) |
| Reduced dose OAC | NA | 84 430 (36.3%) | 16 664 (54.0%) | 32 410 (39.3%) | 24 065 (29.4%) | 11 311 (30.0%) |
| **Comorbidities** | | | | | | |
| Hypertension | 39 216 (60.3%) | 152 407 (65.5%) | 20 020 (65.0%) | 52 359 (63.5%) | 56 103 (68.5%) | 23 925 (63.5%) |
| Coronary artery disease | 15 197 (23.4%) | 39 159 (16.8%) | 4669 (15.2%) | 13 288 (16.1%) | 15 040 (18.4%) | 6162 (16.4%) |
| Congestive heart failure | 10 336 (15.9%) | 34 570 (14.9%) | 3812 (12.4%) | 11 636 (14.1%) | 13 943 (17.0%) | 5179 (13.8%) |
| Valvular heart disease | 12 882 (19.7%) | 27 864 (12.0%) | 3314 (10.8%) | 8715 (10.6%) | 11 068 (13.5%) | 4767 (12.7%) |
| Peripheral artery disease | 7437 (11.4%) | 17 310 (7.4%) | 2097 (6.8%) | 5468 (6.6%) | 7078 (8.6%) | 2666 (7.1%) |
| Dyslipidaemia | 36 396 (55.9%) | 130 685 (56.2%) | 17 877 (58.0%) | 44 458 (53.9%) | 47 446 (58.0%) | 20 904 (55.5%) |
| Chronic kidney disease | 9142 (14.0%) | 24 582 (10.6%) | 2006 (6.5%) | 7459 (9.1%) | 10 920 (13.3%) | 4196 (11.1%) |
| Chronic liver disease | 2751 (4.2%) | 7432 (3.2%) | 836 (2.7%) | 2583 (3.1%) | 2715 (3.3%) | 1297 (3.4%) |
| Chronic lung disease | 8871 (13.6%) | 27 547 (11.8%) | 3278 (10.6%) | 9698 (11.8%) | 10 427 (12.7%) | 4144 (11.0%) |
| Obstructive sleep apnoea | 2509 (3.9%) | 8768 (3.8%) | 1045 (3.4%) | 3006 (3.6%) | 3123 (3.8%) | 1594 (4.2%) |
| Cancer | 6455 (9.9%) | 24 908 (10.7%) | 2803 (9.1%) | 8527 (10.3%) | 8977 (11.0%) | 4601 (12.2%) |
| Upper GI tract disorder | 5452 (8.4%) | 16 511 (7.1%) | 1908 (6.2%) | 5904 (7.2%) | 6424 (7.8%) | 2276 (6.0%) |
| Lower GI tract disorder | 4489 (6.9%) | 16 592 (7.1%) | 1991 (6.5%) | 5726 (6.9%) | 6069 (7.4%) | 2806 (7.5%) |
| Diabetes mellitus | 24 165 (37.1%) | 72 645 (31.2%) | 8695 (28.2%) | 24 296 (29.5%) | 28 030 (34.2%) | 11 623 (30.9%) |
| Thyroid disease | 9556 (14.7%) | 33 714 (14.5%) | 4246 (13.8%) | 11 981 (14.5%) | 12 615 (15.4%) | 4871 (12.9%) |
| Anaemia | 6913 (10.6%) | 17 646 (7.6%) | 1793 (5.8%) | 5868 (7.1%) | 7181 (8.8%) | 2804 (7.4%) |
| Osteoporosis | 4118 (6.3%) | 16 572 (7.1%) | 2102 (6.8%) | 5860 (7.1%) | 6073 (7.4%) | 2537 (6.7%) |
| Dementia | 2948 (4.5%) | 12 542 (5.4%) | 1393 (4.5%) | 4339 (5.3%) | 5059 (6.2%) | 1751 (4.6%) |
| Parkinson's disease | 1692 (2.6%) | 7111 (3.1%) | 926 (3.0%) | 2357 (2.9%) | 2758 (3.4%) | 1070 (2.8%) |
| History of falling | 4286 (6.6%) | 19 160 (8.2%) | 1979 (6.4%) | 5818 (7.1%) | 8161 (10.0%) | 3201 (8.5%) |
| Frailty | 14 480 (22.2%) | 70 716 (30.4%) | 8405 (27.3%) | 22 735 (27.6%) | 28 898 (35.3%) | 10 678 (28.4%) |
| Prior thromboembolism | 9385 (14.4%) | 31 434 (13.5%) | 5482 (17.8%) | 8501 (10.3%) | 13 844 (16.9%) | 3608 (9.6%) |
| Prior MB/CRNMB | 4374 (6.7%) | 12 930 (5.6%) | 1544 (5.0%) | 4116 (5.0%) | 5166 (6.3%) | 2104 (5.6%) |
| **Comedication** | | | | | | |
| Rate control therapy | 35 648 (54.8%) | 151 992 (65.3%) | 19 868 (64.5%) | 52 217 (63.4%) | 55 118 (67.3%) | 24 789 (65.8%) |
| Beta blockers | 33 784 (51.9%) | 143 934 (61.8%) | 18 792 (61.0%) | 49 105 (59.6%) | 52 340 (63.9%) | 23 697 (62.9%) |
| Verapamil, diltiazem | 2253 (3.5%) | 8882 (3.8%) | 1213 (3.9%) | 3422 (4.2%) | 3064 (3.7%) | 1183 (3.1%) |
| Digoxin | 3825 (5.9%) | 22 015 (9.5%) | 2741 (8.9%) | 7399 (9.0%) | 8388 (10.2%) | 3487 (9.3%) |
| Rhythm control therapy | 14 769 (22.7%) | 75 430 (32.4%) | 10 266 (33.3%) | 28 255 (34.3%) | 25 841 (31.6%) | 11 068 (29.4%) |
| Class I AAD | 3604 (5.5%) | 23 031 (9.9%) | 3342(10.8%) | 8864 (10.8%) | 7015 (8.6%) | 3810 (10.1%) |
| Class III AAD | 12 110 (18.6%) | 57 976 (24.9%) | 7745 (25.1%) | 21 679 (26.3%) | 20 548 (25.1%) | 8004 (21.3%) |
| Antiplatelet | 24 707 (38.0%) | 100 525 (43.2%) | 13 362 (43.4%) | 34 562 (41.9%) | 36 611 (44.7%) | 15 990 (42.5%) |
| Acetylsalicylic acid | 22 987 (35.3%) | 93 370 (40.1%) | 12 481 (40.5%) | 32 329 (39.2%) | 33 894 (41.4%) | 14 666 (38.9%) |
| P2Y12 inhibitor | 3753 (5.8%) | 14 470 (6.2%) | 1747 (5.7%) | 4418 (5.4%) | 5535 (6.8%) | 2770 (7.4%) |
| ACE inhibitor/ARB | 30 623 (47.1%) | 117 322 (50.4%) | 15 559 (50.5%) | 41 022 (49.8%) | 42 440 (51.8%) | 18 301 (48.6%) |
| DHP calcium channel blocker | 19 015 (29.2%) | 70 591 (30.3%) | 9055 (29.4%) | 23 693 (28.7%) | 26 622 (32.5%) | 11 221 (29.8%) |

**TABLE 1** (Continued)

| Patient characteristics | VKA ($n = 65\,079$) | NOAC | | | | |
|---|---|---|---|---|---|---|
| | | Overall ($n = 232\,739$) | Dabigatran ($n = 30\,813$) | Rivaroxaban ($n = 82\,411$) | Apixaban ($n = 81\,857$) | Edoxaban ($n = 37\,658$) |
| Loop diuretic | 20 794 (32.0%) | 66 508 (28.6%) | 7633 (24.8%) | 23 170 (28.1%) | 25 446 (31.1%) | 10 259 (27.2%) |
| Non-loop diuretic | 21 201 (32.6%) | 83 683 (36.0%) | 10 834 (35.2%) | 29 219 (35.5%) | 30 257(37.0%) | 13 373 (35.5%) |
| Proton pump inhibitor | 27 585 (42.4%) | 94 000 (40.4%) | 11 560 (37.5%) | 32 360 (39.3%) | 34 685 (42.4%) | 15 395 (40.9%) |
| NSAID | 17 411 (26.8%) | 55 370 (23.8%) | 7444 (24.2%) | 20 553 (24.9%) | 18 563 (22.7%) | 8810 (23.4%) |
| Oral corticosteroids | 14 779 (22.7%) | 47 129 (20.2%) | 5632 (18.3%) | 16 859 (20.5%) | 16 820 (20.5%) | 7818 (20.8%) |
| SSRI/SNRI | 8734 (13.4%) | 28 024 (12.0%) | 3583 (11.6%) | 10 196 (12.4%) | 10 355 (12.7%) | 3890 (10.3%) |
| **Clinical risk score** | | | | | | |
| $CHA_2DS_2$-VASc score | 3.2 ± 2.0 | 3.5 ± 1.8 | 3.5 ± 1.7 | 3.3 ± 1.7 | 3.8 ± 1.8 | 3.3 ± 1.7 |
| Score 0/1 (men/women) | 8373 (12.9%) | 11 233 (4.8%) | 1286 (4.2%) | 5255 (6.4%) | 2595 (3.2%) | 2097 (5.6%) |
| Score 1/2 (men/women) | 10 130 (15.6%) | 26 195 (11.3%) | 3400 (11.0%) | 10 030 (12.2%) | 7684 (9.4%) | 5080 (13.5%) |
| Score ≥2/≥3 (men/women) | 46 576 (71.6%) | 195 311 (83.9%) | 26 126 (84.8%) | 67 126 (81.5%) | 71 577 (87.4%) | 30 481 (80.9%) |
| HAS-BLED score | 2.3 ± 1.4 | 2.5 ± 1.2 | 2.5 ± 1.2 | 2.4 ± 1.2 | 2.7 ± 1.2 | 2.4 ± 1.2 |
| Score ≥3 | 27 072 (41.6%) | 112 602 (48.4%) | 14 809 (48.1%) | 37 342 (45.3%) | 43 341 (52.9%) | 17 110 (45.4%) |
| Charlson Comorbidity Index | 4.1 ± 2.5 | 4.4 ± 2.3 | 4.3 ± 2.1 | 4.2 ± 2.3 | 4.7 ± 2.3 | 4.4 ± 2.4 |
| **Prescriber** | | | | | | |
| Primary care physician | 38 564 (59.3%) | 84 695 (36.4%) | 11 594 (37.6%) | 34 119 (41.4%) | 28 178 (34.4%) | 10 804 (28.7%) |
| Cardiologist | 12 225 (18.8%) | 93 856 (40.3%) | 12 726 (41.3%) | 30 615 (37.1%) | 32 183 (39.3%) | 18 331 (48.7%) |
| Other physician | 14 290 (22.0%) | 54 188 (23.3%) | 6493 (21.1%) | 17 676 (21.4%) | 21 496 (26.3%) | 8523 (22.6%) |

*Note*: Data shown as mean ± standard deviation or counts and percentages. Incident VKA users included 31 447 acenocoumarol, 17 807 warfarin and 15 825 phenprocoumon users.

Abbreviations: AAD, antiarrhythmic drug; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CRNMB, clinically relevant non-major bleeding; DHP, dihydropyridine; GI, gastrointestinal; MB, major bleeding; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VKA, vitamin K antagonist.

Incident NOAC use increased from 27–29 to 39–40 users/10 000 persons (59.7% to 92.2% of OAC users), whereas incident VKA use decreased from 18–20 to 3–4 users/10 000 persons during the study period. NOACs were already more frequently initiated than VKAs in OAC initiators in 2013.

Incident rivaroxaban and dabigatran use consistently decreased over time, whereas incident use of apixaban increased from 2013 to 2016, and of edoxaban from 2016 to 2019 (Figure 2B). Since 2016, apixaban was the most frequently initiated NOAC, whereas edoxaban was the second most initiated NOAC since July 2017. The decline in incident VKA use was comparable for each VKA type (Figure S2A). Trends were consistent when restricting the study population to recently hospitalized OAC-naïve subjects with an ICD-coded hospital discharge diagnosis of AF ($n = 136\,385$) (Figure S3).

## 3.3 | Prevalent use

Prevalent OAC use increased from 337 to 435 users/10 000 persons ≥45 years old from 2013 to 2019 (29.1% increase), driven by an increase in NOAC use (86 to 351 users/10 000 persons; 25.5% to 80.6% of OAC users), while prevalent VKA use decreased (251 to 84 users/10 000 persons) (Figure 3A). Prevalent NOAC use surpassed VKA use from July 2015 onwards.

The increase in NOAC users was initially driven by increasing rivaroxaban use that peaked in 2016, followed by consistently increasing apixaban and edoxaban use from 2013 and 2016 onwards, respectively (Figure 3B). Dabigatran use remained stable over time. Since 2018, apixaban was the most prevalently used NOAC, followed by rivaroxaban, edoxaban and dabigatran. The decline in prevalent VKA use was comparable for each VKA type (Figure S2B). Trends were consistent among OAC-treated subjects with an ICD-coded hospital discharge diagnosis of AF ($n = 177\,054$) (Figure S4).

## 3.4 | Trends by age, sex and prescriber

While VKAs were more frequently initiated in younger (<75 years) than older patients (Figure 4A), the number of AF patients prevalently using (N)OACs was higher in the general population aged 75 years or above *vs.* those aged 45 up to 75 years (Figure 4B). From 2013 to 2019, the number of prevalent OAC users increased with 35.8% in ≥75-year-old AF patients (201 to 273 users/10 000

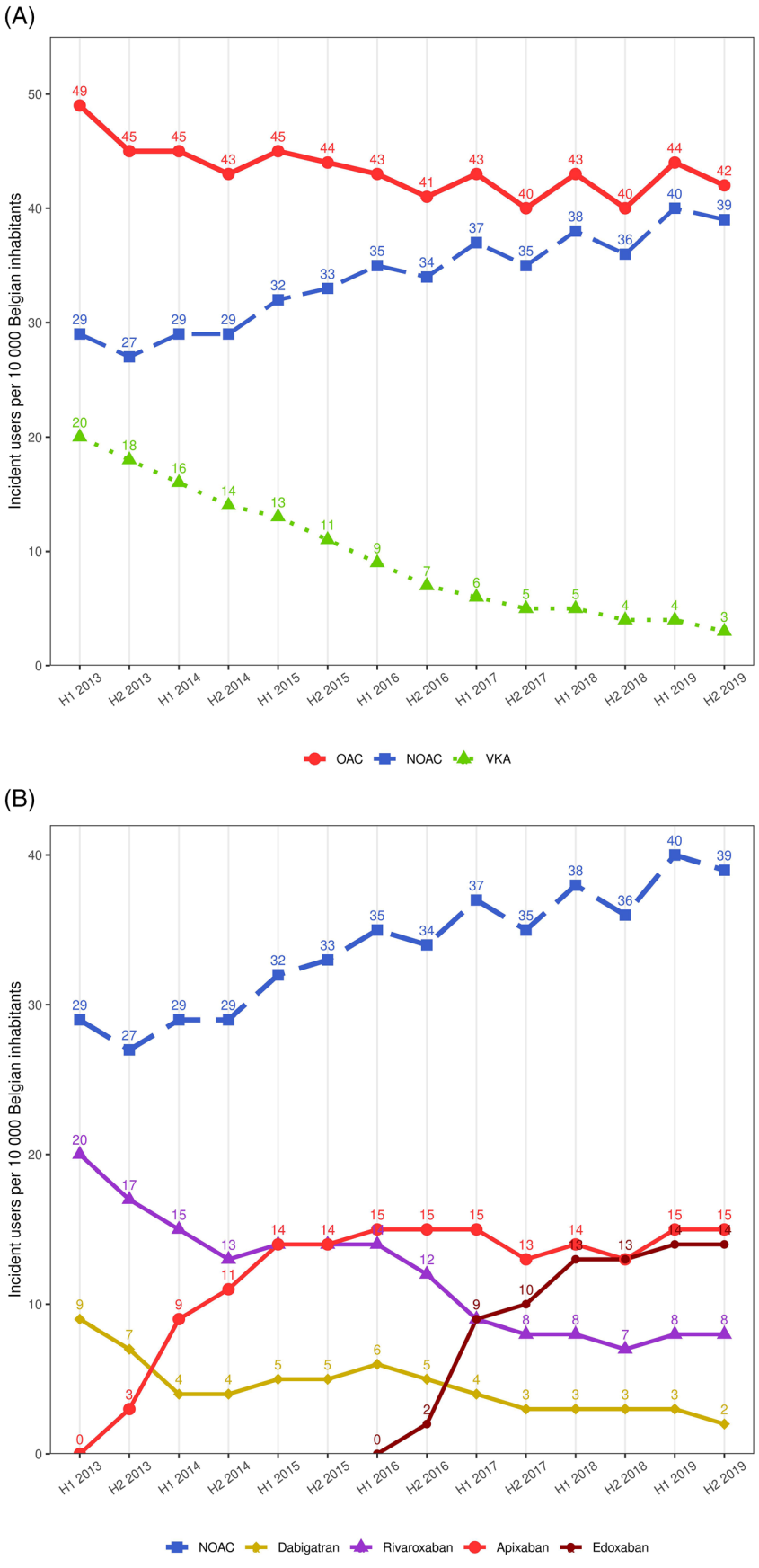


**FIGURE 2** Temporal trends in incident use of (A) OACs, NOACs and VKAs ($n$ = 297 818, 232 739 and 65 079, respectively) and (B) different NOAC types (82 411 rivaroxaban, 81 857 apixaban, 37 658 edoxaban and 30 813 dabigatran users) in AF patients in Belgium from 2013 to 2019 (number of users per 10 000 OAC-naïve Belgian inhabitants ≥45 years old). AF, atrial fibrillation; H1/H2, first/second half-year; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

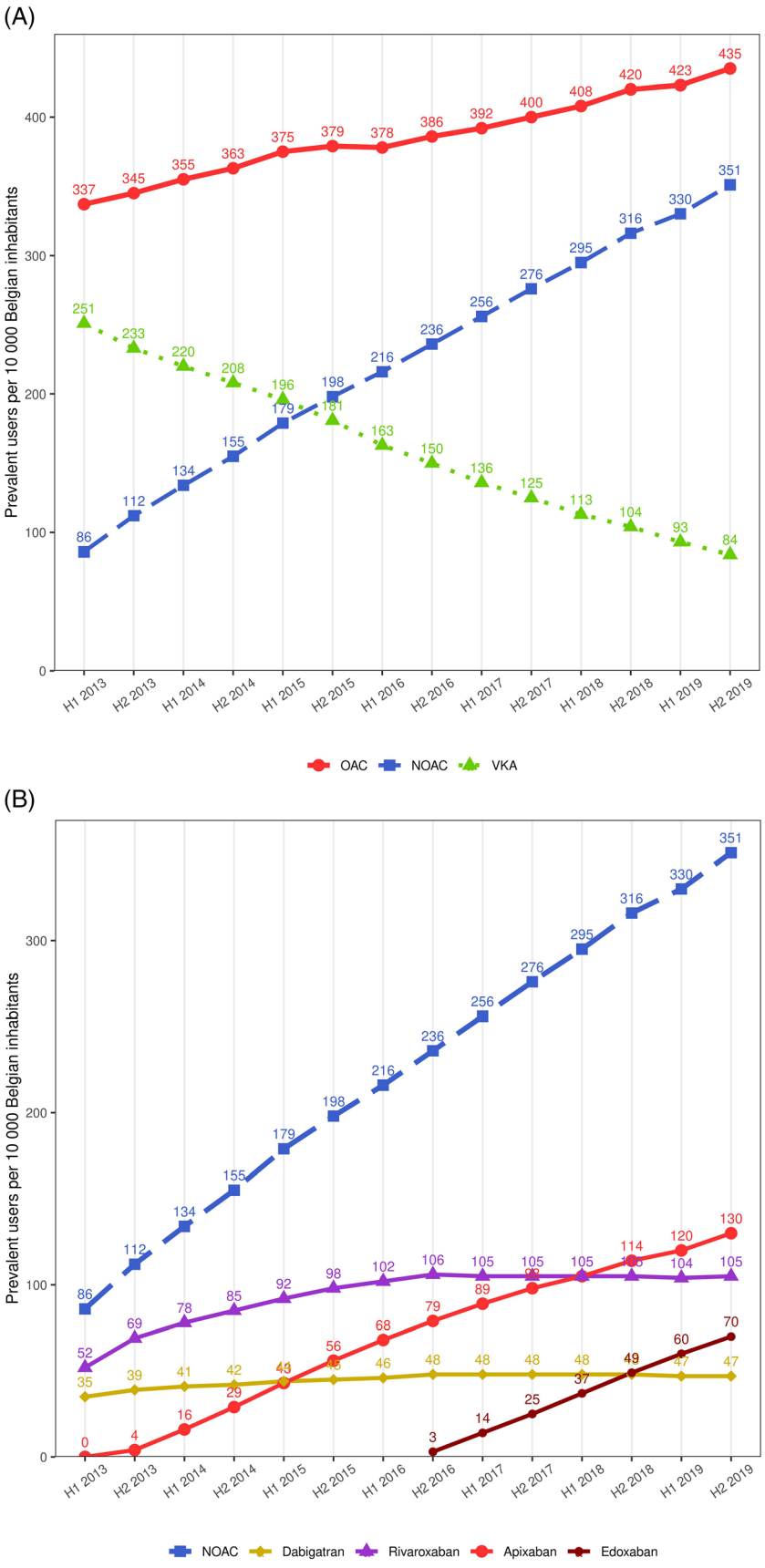


**FIGURE 3** Temporal trends in prevalent use of (A) OACs, NOACs and VKAs ($n$ = 448 661, 260 184 and 188 477, respectively) and (B) different NOAC types (97 357 rivaroxaban, 81 882 apixaban, 43 274 dabigatran and 37 671 edoxaban users) in AF patients in Belgium from 2013 to 2019 (number of users per 10 000 Belgian inhabitants ≥45 years old). AF, atrial fibrillation; H1/H2, first/second half-year; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

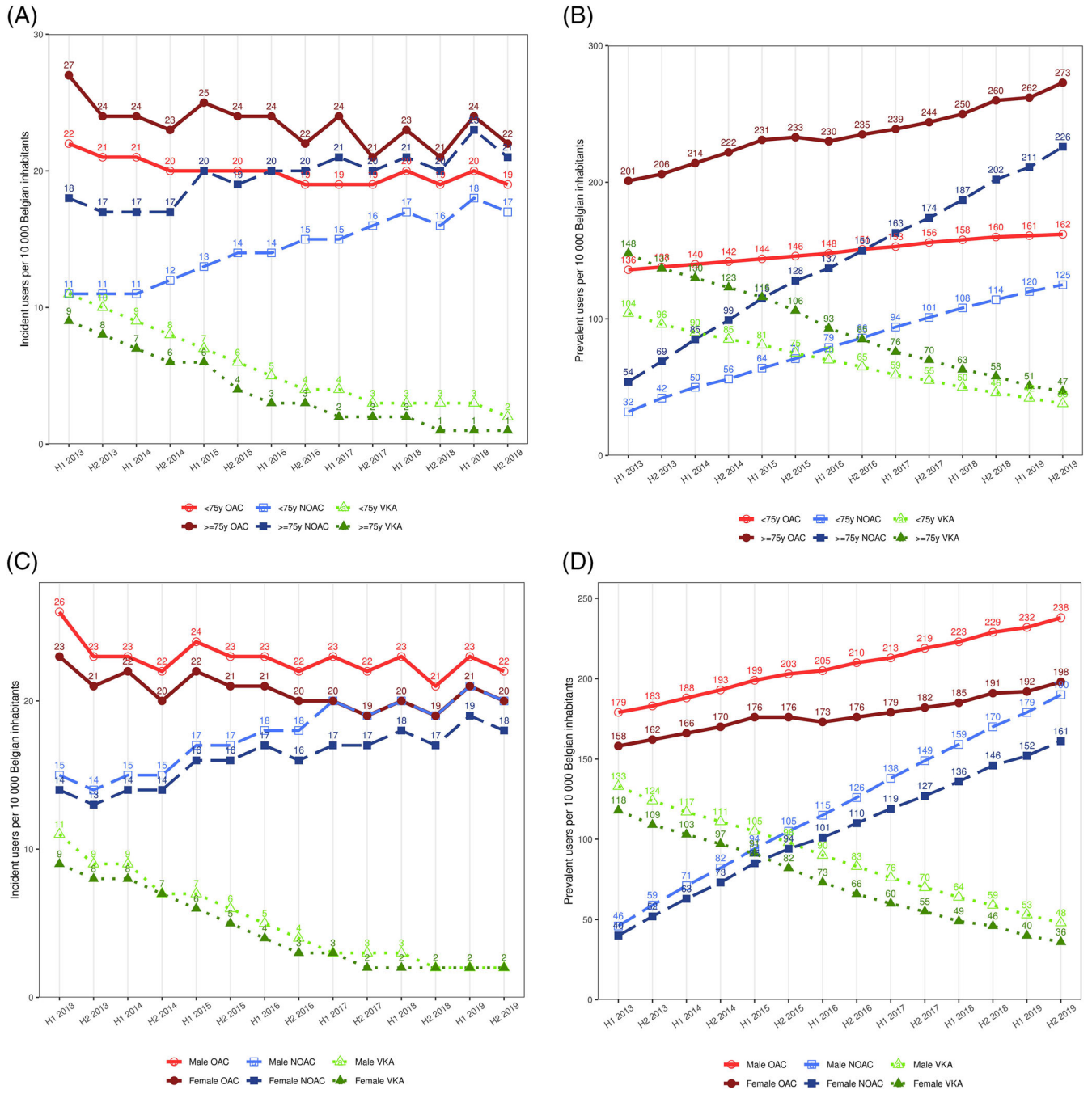


**FIGURE 4** Temporal trends in the use of OACs, NOACs and VKAs in AF patients in Belgium from 2013 to 2019, stratified by age (<75 and ≥75 years) for (A) incident and (B) prevalent use and by sex (male and female users) for (C) incident and (D) prevalent use (number of users per 10 000 Belgian inhabitants ≥45 years old). AF, atrial fibrillation; H1/H2, first/second half-year; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

persons) and with 19.1% in those aged <75 years (136 to 162 users/10 000 persons).

(N)OACs were more frequently initiated and used in male than female AF subjects in the general population ≥45 years old (Figure 4C, D). From 2013 to 2019, the number of prevalent OAC users increased with 33.0% in male (179 to 238 users/10 000 persons) and 25.3% in female AF patients (158 to 198 users/10 000 persons).

Although OACs were slightly more initiated and used in female than male AF subjects ≥75 years old, incident and prevalent OAC use was substantially higher in male than female AF subjects 45–<75 years old (Figure S5A, B). From 2013 to 2019, the number of prevalent OAC users increased with 42.6% in male (94 to 134 users/10 000 persons) and 28.7% in female AF patients ≥75 years old (108 to 139 users/10 000 persons) and with 22.4% in male (85 to 104 users/10 000 persons) and 13.7% in female AF

patients <75 years old (51 to 58 users/10 000 persons) (Figure S5B).

The number of OACs initiated by primary care physicians decreased from 2013 to 2019 (24 to 15 new users/10 000 persons), whereas prescriptions by cardiologist were stable (15 to 17 users/10 000 persons), which made cardiologists the most frequent initiators of anticoagulants by the end of 2019. Other secondary care physicians initiated anticoagulants more frequently over time (from 8–9 to 11–12 new users/10 000 persons) (Figure S6).

### 3.5 | Factors associated with OAC choice

After multivariable adjustment, factors associated with significantly higher odds of being initiated on NOACs than VKAs were having a more recent prescription (July 2016–2019 *vs*. 2013–June 2016) or a prescription from cardiologists or other secondary care physicians compared to primary care physicians; being older (≥75 *vs*. <75 years), multimorbid (CCI ≥ 4 *vs*. <4), frail, dement or having recently fallen; having hypertension, heart failure or lower gastrointestinal tract disorders; and using antiplatelets (Figure 5). Factors associated with significantly lower odds of NOAC *vs*. VKA initiation were having valvular heart disease, CKD, CAD, PAD, diabetes mellitus, liver disease, prior major or clinically relevant non-major bleeding or upper gastrointestinal tract disorders; using SSRIs/SNRIs, corticosteroids or proton pump inhibitors; and being female compared to being male (OR 0.95, 95% CI [0.93–0.97]). Other factors (e.g., thromboembolism) did not significantly affect the choice of OAC after multivariable adjustment.

Results were consistent after stratifying by age category, sex, time period and prescriber type (Table S2). However, liver disease, cancer and upper gastrointestinal tract disorders were associated with significantly lower odds of NOAC *vs*. VKA initiation in 2013–2016, whereas with similar to higher odds in 2016–2019. Moreover, the significantly lower odds of NOAC *vs*. VKA initiation in female compared to male AF patients aggravated over time (OR 0.96, 95% CI [0.94–0.99] in 2013–2016; OR 0.92, 95% CI [0.89–0.96] in 2016–2019) (Table S2). Compared to men, women had significantly lower odds of NOAC *vs*. VKA initiation when aged <75 years (OR 0.93, 95% CI [0.90–0.95]) or when being prescribed by primary care physicians (OR 0.86, 95% CI [0.83–0.88]), whereas a non-significantly different odds ratio when aged ≥75 years (OR 0.97, 95% CI [0.95–1.00], *P* value = .09) and significantly higher odds when being prescribed by cardiologists (OR 1.11, 95% CI [1.05–1.17]) or other physicians (OR 1.07, 95% CI [1.02–1.12]).

## 4 | DISCUSSION

In our nationwide cohort study, we observed an increasing proportion of OAC users from 2013 to 2019, driven by a strong rise of NOAC users ≥75 years old. OAC use in female AF patients aged below

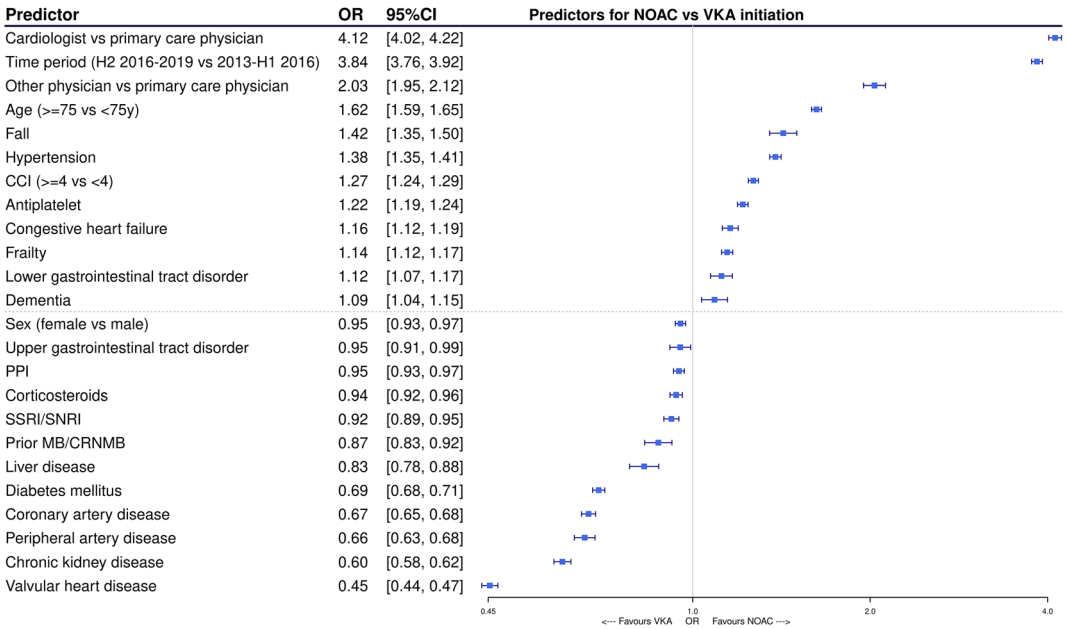


**FIGURE 5** Factors significantly associated with NOAC *vs*. VKA initiation in OAC-naïve AF patients after multivariable adjustment, using multivariable logistic regression with backward elimination. Factors not significantly associated with the choice of OAC after multivariable adjustment (e.g., prior thromboembolism and cancer) were removed from the final model and are not presented. AF, atrial fibrillation; CCI, Charlson Comorbidity Index; CI, confidence interval; CRNMB, clinically relevant non-major bleeding; H1/H2, first/second half-year; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; PPI, proton pump inhibitor; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor; VKA, vitamin K antagonist

75 years followed in primary care seems to be lagging. Among nearly 450 000 AF patients treated with oral anticoagulants, the prescriber type and the patient's age and multimorbid status largely defined the preference for NOACs over VKAs.

## 4.1 | Temporal trends

Since we have demonstrated an almost one-third increase in the number of AF patients treated with OACs in the general Belgian population from 2013 to 2019, especially among older and male AF patients, the introduction of NOACs and updated guideline recommendations did have a profound impact on real-world, guideline-adherent OAC prescribing in AF patients on a full-population scale in Belgium. Incident and prevalent NOAC use have considerably increased over time and represented 92% and 81% of OAC users in 2019, respectively. NOAC initiation and use surpassed VKA use more quickly in Belgium than worldwide.[7]

Increased anticoagulant prescribing and the recent paradigm shift in OAC choice have been observed in several other countries.[7–10,20,21,26] Factors contributing to the increased prevalent use of anticoagulants include the increasing prevalence and detection of AF, availability of NOACs with their practical advantages, increased persistence on anticoagulant treatment thanks to the possibility to switch between OACs in case of intolerance or side effects, updated guideline recommendations (e.g., use of $CHA_2DS_2$-VASc instead of $CHADS_2$ score and discouragement from using antiplatelets for stroke prevention in AF)[1,3] and intensive direct-to-prescriber marketing.[1,2,7,27] Moreover, improved survival from AF-related outcomes and associated cardiovascular comorbidities may have also contributed, given that NOACs are associated with significantly lower thromboembolic and mortality risks in older AF patients than VKAs.[28] Lastly, broadened reimbursement criteria for NOACs may have also played a role. Initially, NOACs were only reimbursed in AF patients at high thromboembolic risk in Belgium,[29] followed by additional reimbursement in AF patients at intermediate thromboembolic risk since May 2020.[30] However, as reimbursement criteria were broadened after our study period, this did less likely impact our results.

In Belgium, NOAC uptake was remarkably fast, as already in 2013 60% of incident OAC users were initiated on NOACs. 'Compassionate use' programmes, which allow the use of drugs with an approved European indication before they are commercially available, may have contributed to this trend, as NOACs have been available to Belgian cardiologists for clinical use since 2011, resulting in early experiences with NOACs.[5,6] However, overall incident anticoagulant use did not increase over time, as opposed to worldwide trends.[7] It is possible that incident OAC use in Belgium increased before the start of our study and resulted in consistently high anticoagulant initiation between 2013 and 2019, as other nationwide studies observed the steepest increase in incident OAC use in 2010–2011.[10,20]

Following their respective approval in September 2013 and October 2016, the use of apixaban and edoxaban rapidly increased, whereas the use of dabigatran and rivaroxaban (respective approval in August and September 2012) stabilized or decreased.[29] Consequently, apixaban became the most frequently initiated (since 2016) and prevalently used (since 2018) NOAC. Similar shifts in the choice of NOAC over time were observed in other studies.[8,9,21,26,31] Although prior studies lacked sufficient numbers of edoxaban users, we could demonstrate that edoxaban use followed a similar increasing trend as apixaban. This may be due to a new-drug effect in the first year(s) after reimbursement, which was also observed after approval of dabigatran (2010–2012) and rivaroxaban (2011–2014) in other studies.[9,21,26] Moreover, perception of favourable safety profiles of apixaban and edoxaban (especially in older AF patients),[28] differences in renal clearance (highest for dabigatran while lowest for apixaban),[3] early reports of potentially increased risks of myocardial infarction[32] and dyspepsia[33] with dabigatran (although not replicated in later research[34]), and differences in direct-to-prescriber marketing by pharmaceutical companies may have contributed to the preferential prescribing of apixaban and edoxaban over time.[21,26–28]

## 4.2 | Predictors of OAC choice

Several factors significantly influenced the anticoagulant choice in OAC-naïve AF patients. Compared to VKAs, NOACs were more frequently initiated by secondary than primary care physicians, in the second part (July 2016–2019) than the first part of the study period (2013–June 2016), in older AF patients with age-associated traits (e.g., frailty), hypertension, heart failure or lower gastrointestinal tract disorders and among antiplatelet users after multivariable adjustment. Preferential prescribing of NOACs in more recent years, irrespective of patient or physician characteristics, is in line with guidelines expressing a preference for NOACs over VKAs in the general AF population.[1,3] Likewise, NOAC use in older, geriatric AF patients seems appropriate, given the superior effectiveness and at least non-inferior safety profile of NOACs compared to VKAs in AF patients ≥75 years old.[28] The preference for NOAC initiation in subjects with previous antiplatelet use, as previously observed,[35] could be driven by AF patients initially using antiplatelets for thromboembolic prevention due to (relative) contraindications for VKAs. Given the significantly higher thromboembolic and similar major bleeding risks of antiplatelets compared to OACs, it is appropriate and guideline-recommended to use (N)OACs in AF patients instead.[3,36] The higher odds of NOAC initiation in subjects with lower gastrointestinal tract disorders is remarkable, given the higher gastrointestinal bleeding risk with NOACs than VKAs.[3] However, subjects with upper gastrointestinal tract disorders did have lower odds of NOAC initiation.

Moreover, being prescribed by cardiologists or other secondary care physicians was the strongest independent predictor of NOAC preference over VKA in new cases. Faster NOAC uptake and increased anticoagulant prescribing by specialists in contrast to slower NOAC uptake and reduced OAC initiation by primary care physicians, is in line with prior research.[21,26,27,31,35] Reasons for specialists

adopting new therapies faster include being more up to date with results from recent studies, better guideline adherence, availability of 'compassionate use' programmes for cardiologists,[6] more experience with NOACs and clinical pharmacist interventions in secondary care.[5,26,27,31,37]

However, cardiovascular, renal and hepatic comorbidities were independent predictors of VKA preference over NOAC in new cases, as observed before.[11,24] This may be due to some comorbidities requiring dose reduction of NOACs or contraindicating their use, namely valvular heart disease (e.g., contraindicated in mechanical valves, moderate–severe mitral stenosis and in the first 8–12 weeks after bioprosthetic heart valve replacement),[3] renal disease and liver disease (e.g., contraindicated if liver cirrhosis Child–Pugh (B–)C).[3] Furthermore, predominantly thromboembolic risk factors such as vascular disease and diabetes, but also prior bleeding and bleeding-related drug use, were independent predictors of VKA initiation, in line with previous research.[26,31] This may be driven by the possibility to monitor the anticoagulant effect of VKAs and to closely follow up treatment adherence of patients at high thromboembolic and/or bleeding risk using the INR.[27,31] Likewise, the availability of antidotes for VKAs may have influenced the anticoagulant choice in subjects with prior bleeding and bleeding-related drug use, although reversal agents for NOACs have emerged.[3,31] However, market approval of **idarucizumab** in 2016 did not affect dabigatran prescription rates in our study.

## 4.3 | (N)OAC underuse in women

After multivariable adjustment, female subjects still had 5% significantly lower odds of NOAC instead of VKA initiation compared to men, especially in younger AF patients <75 years old and when being prescribed by primary care physicians. Likewise, the increase in AF patients prevalently using (N)OACs in the general population was more pronounced in male than female subjects over time. Higher rates of (N)OAC use in male than female AF subjects have also been observed in other studies,[5,8–11,21,24,26,35] and even in the phase III randomized controlled trials investigating NOACs, females were underrepresented (35–40% of included subjects).[33,38–41]

These results are surprising, as female sex is a thromboembolic risk factor included in the $CHA_2DS_2$-VASc score.[3] Reasons behind the lower (N)OAC prescription rates in women are not well established and necessitate further research. Besides the age-adjusted incidence and prevalence of AF being higher in men,[2,3] contributing factors may include a lower detection and undertreatment of AF in women (e.g., women are less and later referred for ablation than men[42]), and a higher perceived bleeding risk and underestimated net clinical benefit of OACs due to females being older and having more comorbidities at time of AF diagnosis.[3,10,39–41] Moreover, studies showing that the increased thromboembolic risk among female AF patients may be limited to older women with other risk factors, and that female sex should be considered as a risk modifier rather than a risk factor, may have resulted in physicians underestimating the increased thromboembolic risk of female AF patients.[1,39,43] However, since higher endogenous factor Xa levels (reflecting a higher thromboembolic potential) and worse stroke-related outcomes have been observed in female compared to male AF patients, women do benefit from anticoagulation.[3,40,43,44] Since the risk–benefit profile of NOACs is similar in men and women, and poorer INR control has been demonstrated in warfarin-treated female AF patients compared to men, NOACs should also be preferred over VKAs in women.[33,38–41] Therefore, efforts targeted at (primary care) physicians may be needed to increase the awareness of the thromboembolic risk of being female and improve the knowledge of the expected risk–benefit profile of NOACs in female AF patients.

## 4.4 | Strengths and limitations

Strengths of this first nationwide cohort study on AF-related anticoagulant use in Belgium include the 7-year follow-up, investigation of real-world prescribing on a full-population scale including a high number of edoxaban users (often insufficient numbers in prior research) and difficult-to-reach subgroups (e.g., subjects with dementia), and assessment of anticoagulant dispensing in ambulatory and hospital care. Several limitations should be mentioned. First, inherent to our observational design using healthcare databases, coding errors, misclassification bias and unmeasured confounding may be present. However, by identifying comorbidities based on ICD, ATC and/or medical procedure codes assessed in ambulatory and hospital care, and by accounting for missing data with multiple imputation, confounding was reduced. Second, due to the lack of lifestyle characteristics (e.g., weight, smoking and alcohol consumption) and laboratory values (e.g., renal function and INR), (in)appropriate NOAC dosing could not be evaluated. Third, although OAC-treated patients with competing treatment indications were excluded (e.g., pulmonary embolism), subjects were not required to have an ICD-coded hospital discharge diagnosis of AF to be included, as this would have limited our study population to recently hospitalized AF patients and excluded AF patients treated exclusively in primary or ambulatory care.[18] Nevertheless, trends were consistent when specifically investigating subjects with an ICD-coded diagnosis of AF ≤1 year before or ≤90 days after the index date. Fourth, due to the exclusion of OAC-treated patients with competing treatment indications, our results should not be extrapolated to patients using (N)OACs for prevention or treatment of venous thromboembolism. Fifth, due to specific inclusion of OAC-treated AF patients, we could not assess the proportion of high-risk AF patients not receiving anticoagulation. Sixth, we did not exclude OAC-treated subjects at low thromboembolic risk ($CHA_2DS_2$-VASc score 0 in men, 1 in women), given the potential underestimation of risk factors (e.g., hypertension) and influence of other physician-perceived thromboembolic risk factors not included in the $CHA_2DS_2$-VASc score (e.g., cancer). However, low-risk patients undergoing cardioversion or catheter ablation with a temporary need for anticoagulation may have been included. Seventh, the number of incident OAC users may have been overestimated at the beginning of our study period (e.g., 2013), since subjects having used and

discontinued an OAC >1 year before the start of our study would not have been identified as OAC-experienced. Eighth, anticoagulant use was estimated based on dispensing of OACs, not the patient's actual intake. Lastly, AF patients using free (NOAC) drug samples were not identified.

## 5 | CONCLUSION

Prevalent anticoagulant use in Belgium increased almost one third from 2013 to 2019, whereas incident use remained stable over time. NOAC use quickly exceeded VKA use, and apixaban is currently the most initiated and prevalently used NOAC. NOACs were more frequently prescribed by cardiologists and to older AF patients, whereas VKAs were more frequently initiated in patients with cardiovascular, renal and hepatic comorbidities. A treatment gap seems to be emerging for female AF patients <75 years old followed in primary care. Therefore, efforts to reduce potential (N)OAC underuse in women may be warranted.

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### COMPETING INTERESTS

There are no competing interests to declare.

### AUTHOR CONTRIBUTIONS

Maxim Grymonprez and Lies Lahousse contributed to the concept and design of the study. Maxim Grymonprez performed the statistical analysis, interpretation and writing under the supervision of Lies Lahousse, Tine L. De Backer, Andreas Capiau, Delphine Vauterin, Els Mehuys, Koen Boussery, Stephane Steurbaut and Lies Lahousse revised the manuscript critically. All authors contributed to the article and approved the final manuscript.

### DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared for privacy reasons and according to local laws and regulations. Any further inquiries regarding data availability should be directed to Professor Lies Lahousse (lies.lahousse@ugent.be) or the administrators of the InterMutualistic Agency (IMA) database or Minimal Hospital Dataset.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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