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Trends in oral anticoagulant prescription in patients with nonvalvular atrial fibrillation in Flanders and the impact of switching patients from vitamin K antagonists to DOACS in terms of the burden caused by complications of the disease: a registry-based study

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ABSTRACT

Context: Since the introduction of direct oral anticoagulants (DOACs) for the treatment of nonvalvular atrial fibrillation (Afib), oral anticoagulants (OACs) prescription has evolved.

Aim: We aim first to explore the OACs prescription behaviour in Flanders from 2002 to 2019 before exploring the impact of switching patients from vitamin K antagonists (VKAs) to DOACs in terms of the burden caused by stroke as a complication of non-valvular Afib.

Methods: Data were obtained from INTEGO, a Flemish, general practice-based morbidity registration network. Comprised patients had at least one visit to their GP per year between 2002 and 2019 and a follow-up of at least 1 year after the diagnosis of Afib. Public prices were retrieved from the Belgian Centre for Pharmacotherapeutic Information (BCFI) and the National Institute for Health and Disability Insurance (RIZIV/ INAMI) sites. The number of Disability-Adjusted Life Years (DALYs) was based on the Global Burden of Disease (GBD) literature. The calculation of the Number Needed to Switch (NNSw) was the basis for conducting cost-utility analyses accounting for the global benefit in terms of the cost of prevented stroke/DALY and the cost of switching Flemish ≥ 65 years patients from VKAs to DOACs in two scenarios.

Results: Increased DOAC use has been observed since 2012. The incremental cost effectiveness ratios (ICERs) yielded 553 to 824 €/DALY of prevented stroke.

Conclusion: In this registry-based study, we found a significant positive trend in OAC use in Flanders between 2002 and 2019. Switching to DOACs seems cost-effective compared to a threshold of 20000€/DALY.

KEYWORDS
VKA; DOAC; atrial fibrillation; stroke

Introduction

Atrial fibrillation (Afib) is a type of heart arrythmia characterised by rapid, uncoordinated electrical impulses in the atrium, with a prevalence in the general population approaching 2% [1,2]. Afib is divided into valvular and nonvalvular Afib (NVAF). The former pertains to rheumatic valvular disease or mechanical heart valves [3]. Among the burdensome complications of Afib are ischaemic strokes, whose risk is assessed by the CHA_2DS_2-VASc risk stratification score [1]. The European Society of Cardiology (ESC) guidelines have recommended oral anticoagulants (OACs) as a treatment of choice for Afib, with conclusive evidence of their use in cases of a CHA_2DS_2-VASc score of at least 1 for men and 2 for women [3]. The first OACs were vitamin K antagonists (VKAs). They require frequent haemostatic monitoring because of their narrow therapeutic range, unlike direct oral anticoagulants (DOACs), which are characterized by their predictable pharmacokinetic profile [3].

Compared to warfarin, DOACs significantly reduce the risk of stroke or systemic embolism (SE), all-cause mortality and intracranial haemorrhage but increase the risk of gastrointestinal bleeding [4,5]. Two out of the three Belgian cost-effectiveness analyses concluded that rivaroxaban and dabigatran were cost-effective alternatives to VKAs for stroke and SE prevention [6,7]. For Afib registries, the worldwide, prospective, ongoing GARFIELD-AF showed that 51.4% of newly Afib diagnosed patients received DOAC as a first treatment between 2013 and 2016 [8]. Additionally, in the European EORP-AF registry, the proportion of VKAs was 71.6% out of the 80% of anticoagulated patients as of March 2013 [9]. In Belgium, DOACs have seen a tremendous increase in use since their introduction in the market in 2012 [10]. Until 2017, up to 50% of Belgian patients were still under VKA treatment [11].

In 2016, stroke ranked as the second leading cause of DALYs worldwide. DALYs are composed of years lived with disability (YLDs) and years of life lost due to premature mortality (YLLs). The rate of years of life lost (YLL) due to stroke tremendously increased with age compared to the years lived with disability (YLD),

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especially in old adults [12]. To date, there is no evidence in the literature regarding the global burden of stroke in Belgium, particularly Flanders, where a simulation of a cost-utility analysis would give insights on the benefit of switching old adult Afib patients, both regarding the quality and quantity of life dimensions, from VKAs to DOACs in terms of cost per DALY of prevented stroke. This raises the question of what the benefit is to switching patients aged 65 years or older in Flanders from VKAs to DOACs in terms of cost per DALY of prevented stroke.

We aim first to study the pattern of OAC prescriptions in Flanders based on the INTEGO database, a Flemish computerized morbidity registration network at the Department of General Practice of the University of Leuven, from 2002–2019 and then to conduct cost-utility analyses in terms of the potential benefit, in DALYs, of switching NVAF patients aged 65 years and older from warfarin to DOACs.

Methods

Data collection

Data were collected from the INTEGO database, which gathers longitudinal information from the medical electronic health record software system from general practitioners, centrally storing the data at the Department of General Practice at KU Leuven University in Belgium [13]. The recorded information was classified according to the International Classification of Primary Care (ICPC-2) for new diagnoses and WHO's Anatomical Therapeutic Chemical (ATC) classification system for prescribed drugs. The database includes more than 200000 patients who are representative of the Flemish population in terms of age and sex [13]. Drug and laboratory test costs were retrieved from the Belgian Centre for Pharmacotherapeutic Information (BCFI) and RIZIV/ INAMI sites, respectively, based on 2019 public prices. RIZIV/ INAMI is the National Institute for Health and Disability Insurance, a federal public part of the Belgian social security managing the country's schemes for health insurance and disability benefits. The number of DALYs was based on the Global Burden of Disease literature [14].

Patient selection

For the descriptive part of our study, we gathered data on the annual prevalent and incident Afib cases in Flanders between 2002 and 2019. Comprised patients were those who had at least one visit to their GP per year between 2002 and 2019 and who had a follow-up of at least 1 year after the diagnosis of Afib. For the cost-utility analyses, we are specifically interested in prevalent Afib patients aged 65 years and older under treatment with OACs.

Background variables

Comorbidity variables included the ones used to calculate the CHA_2DS_2-VASc: congestive heart failure/left ventricular dysfunction, history of hypertension, diabetes, history of thromboembolic event (transient ischaemic attack (TIA) or stroke) and history of vascular disease, whether acute myocardial infarction or peripheral artery disease (PAD). For females and 65–74-year-old patients, an additional point was added, and two points were added for patients ≥ 75 years old. CHA_2DS_2-VASc scores were divided into three categories: category 0 points, category 1 point, and category ≥ 2 points.

Treatment

Oral anticoagulants prescriptions

The included VKAs were warfarin, phenprocoumon and acenocoumarol. Four DOACs are reimbursed in Belgium: apixaban, dabigatran etexilate, rivaroxaban and edoxaban.

Co-medications prescriptions

First, cardiovascular medications were considered, and they included antiplatelet agents, angiotensin converting enzyme (ACE) inhibitors, angiotensin II (ATII) antagonists, diuretics and dihydropyridine calcium-channel blockers (CCBs). Furthermore cardiovascular medications often prescribed in AFib were recorded and included all class I antiarrhythmic drugs and the class III antiarrhythmic drug amiodarone, and rate controlling drugs: beta-blockers, non-dihydropyridine CCBs, and digoxin. Secondly, drugs used in the treatment of diabetes were also recorded. The prescription of a comedication was included if the patient had at least two prescriptions of that comedication in one year.

Model structure and outcomes

Since DOACs were introduced into the Belgian market in 2012, we conducted cost-utility analyses for 2012–2019 for two chosen scenarios, both based on the 2019 data numbers from INTEGO. The *first scenario* accounts for the global benefit, in terms of the equation (cost of prevented stroke/DALY), triggered by switching above 65-year-old Afib patients in Flanders from VKAs to DOACs. The *second scenario* estimates the same benefit if all above 65-year-old eligible Afib patients in Flanders including those without anticoagulant treatment were prescribed DOACs. For the latter, as the dual increase in bleeding and thrombotic risk in elderly individuals leads to uncertainty in the prescription of

anticoagulants, we only included patients with a CHA_2DS_2-VASc score of 2 and excluded those who had a bleeding history [Table 1].

We conceptualised the notion of Number Needed to Switch (NNSw) to quantify the number of patients of which the treatment by VKAs has to be substituted by DOAC's in order to prevent one new stroke. NNSw was calculated based on data produced by a systematic review of Caldeira et al. [15]. First, we retrieved the absolute risk reduction from the relative risk of stroke and SE of DOACs compared to VKAs in the above 75-year-old group. From there, we calculated the NNSw as the inverse of ARR. Assuming the risk follows a proportional speed, the yielded NNSw is 47 patients in 1 year [CI 35–78]. Anticoagulation-eligible patients were divided between 2,198 patients under DOACs, 590 patients who received VKAs, and 566 OAC-eligible patients [Figure 1]. The number of VKA users in the INTEGO population in 2019 was divided by the NNSw to obtain the number of prevented strokes per year, while the anticoagulation-free status was divided by the number needed to treat (NNT) of DOACs retrieved from the article entitled 'Apixaban in Patients with Atrial Fibrillation' by Connolly et al. [16]. The confidence interval (CI) calculation around the prevented strokes was calculated as the inverse of the ARR CI. We calculated an ICER for each scenario, using the following formula: $\frac{\Delta cost}{\Delta DALY}$. The denominator is the number of prevented strokes*DALYs of ischemic stroke, and the nominator is the difference of cost between all 590 patients in the register in 2019 under VKAs (747€ person/year) and these same 590 patients if they were switched to DOACs (1500 €/person/year).

Knowing that the burden of ischaemic stroke is 64 DALYs/person in accordance with the 2019 GBD study, we calculated the incremental DALYs by multiplying the burden of ischaemic stroke in DALYs/person by the number of prevented strokes per year in Flanders for 2019 for each scenario.

The total cost of 747€ of VKA/person/year included the cost of the drug and yearly blood monitoring, combining the cost of INR and 15 yearly GP visits according to the Inter Mutualistic Agency (IMA). The mean cost of DOACs accounted for the average cost of a DOAC/person/year, yielding 1500 €/person/year.

Prevalence and incidence calculations

Prevalence figures of chronic disease in general should be interpreted with caution, since in theory they can only go up as new cases are diagnosed, while the previously diagnosed patients continue to be affected. Yearly incident cases were those who were newly diagnosed for Afib during each year studied. The period of the year longs from January the 1st till December 31st of that year. Yearly prevalent cases were the total cases counted each year. INTEGO has developed a validated methodology to relate observed numbers in the registry to the served population. The denominator used to calculate the prevalence and incidence was the Yearly Contact Group (YCG). These are the patients that visited the practice at least once in a given year [17,18].

Statistical analysis

The baseline characteristics of patients with prevalent Afib in the registry were compared over four five-year periods. The P for trend was calculated using the Jonckheere-Terpstra test. A two-tailed probability value $p < 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of patients with Afib in the registry

The total number of patients with Afib was 6,122 between 2002 and 2019, and the number of patients increased in the last five years. Patient BMI was in the overweight range regardless of age (27.4 ± 4.3). A history of hypertension was the most common condition (32.7%, p = 0.8143), followed by renal dysfunction (24.3%, p < 0.0001), history of bleeding (18.9%, p = 0.5172), diabetes (16.3%, p = 0.0032), thromboembolic events (12.4%, p = 0.2479), vascular disease (8.6%, p = 0.3318) and heart failure (8.2%, p = 0.3326). We observed an increase in VKA use between 2007 and 2011, before decreasing since the introduction of DOACs on the Belgian market in 2012. In parallel, an important increase in DOACs was detected since 2011. At the level of cardiovascular medications, beta-blockers are the most widely used drugs among Afib patients (56.9%, p < 0.0001) [Table 1].

Incidence and prevalence of Afib

The prevalence graph displays a striking increase in prevalence over time. An important increase in the above 75-year-old group and consequently in the CHA_2DS_2-VASc ≥ 2 score group was detectable in the last five years [Figure 2]. The highest incidence was in the above 75-year-old patient group [Figure 3]. The overall prevalence of Afib in the patients 65+ increased from 5.3% in 2012 to 9.7% in 2019. During the same period the overall incidence in that age group rose from 0.79% per year, to 1.51% per year (Figures 6 and Figure 7 in the appendix).

Evolution of the number of patients under OACs

In the first year after diagnosis with Afib, we found an important increase in the use of OACs in patients

Table 1. Baseline characteristics of patients with Afib.

Variables	All patients	2002–2006	2007–2011	2011–2015	2015–2019	P*
Patients with Afib	6122	1188	1114	1244	2576	
Baseline characteristics						
Age of patients						
< 65 y.o., n (%)	1307(21.3%)	269(22.6%)	254(22.8%)	276(22.2%)	508(19.7%)	0.0173
65–75 y.o., n (%)	1802(29.4%)	391(32.9%)	346(31.1%)	351(28.2%)	714(27.7%)	0.0005
> 75 y.o., n (%)	3013(49.2%)	528(44.4%)	514(46.1%)	617(49.6%)	1354(52.6%)	<0.0001
Females, n (%)	2840(46.4%)	554(46.6%)	526(47.2%)	577(46.4%)	1183(45.9%)	0.5525
CHA_2DS_2-VASc score at time of diagnosis						
Category 0, n (%)	556(9.1%)	116(9.8%)	111(10%)	107(8.6%)	222(8.6%)	0.1469
Category 1, n (%)	967(9.1%)	210(9.8%)	176(10%)	206(8.6%)	375(8.6%)	0.0211
Category ≥2, n (%)	4599(75.1%)	862(72.6%)	827(74.2%)	931(74.8%)	1979(76.8%)	0.0036
Patient BMI	27.4(4.3)	28.1(4.1)	27.3(4.5)	27.9(4)	27.1(4.3)	No test available
Comorbidities						
Heart failure, n (%)	501(8.2%)	105(8.8%)	93(8.3%)	99(8%)	204(7.9%)	0.3326
History of hypertension, n (%)	2003(32.7%)	365(30.7%)	388(34.8%)	421(33.8%)	829(32.2%)	0.8143
Diabetes, n (%)	1000(16.3%)	148(12.5%)	183(16.4%)	240(19.3%)	429(16.7%)	0.0032
History of thromboembolic event (stroke/TIA), n (%)	762(12.4%)	133(11.2%)	132(11.8%)	178(14.3%)	319(12.4%)	0.2479
Vascular disease (history of myocardial infarction or peripheral artery disease), n (%)	528(8.6%)	89(7.5%)	105(9.4%)	105(8.4%)	229(8.9%)	0.3318
Renal dysfunction, n (%)	1487(24.3%)	238(20%)	276(24.8%)	273(21.9%)	700(27.2%)	<0.0001
Bleeding history, n (%)	1158(18.9%)	223(18.8%)	221(19.8%)	243(19.5%)	471(18.3%)	0.5172
Drug/alcohol consumption, n (%)	179(2.9%)	23(1.9%)	26(2.3%)	36(2.9%)	94(3.6%)	0.0015
Patients' treatment						
VKA, n (%)	1584(25.9%)	438(36.9%)	498(44.7%)	433(34.8%)	215(8.3%)	<0.0001
DOAC, n (%)	1461(23.9%)	0(0%)	0(0%)	319(25.6%)	1142(44.3%)	No test available
Cardiovascular medication						
Antiplatelet agents, n (%)	2308(37.7%)	469(39.5%)	559(50.2%)	496(39.9%)	784(30.4%)	<0.0001
Ace inhibitors/AT2 antagonists, n (%)	2445(39.9%)	402(33.8%)	456(40.9%)	511(41.1%)	1076(41.8%)	<0.0001
Diuretics, n (%)	1893(30.9%)	357(30.1%)	361(32.4%)	393(31.6%)	782(30.4%)	0.8053
Dihydropyridine CCB, n (%)	894(14.6%)	151(12.7%)	190(17.1%)	175(14.1%)	378(14.7%)	0.5452
Antiarrhythmic drugs, n (%)	1591(26%)	359(30.2%)	322(28.9%)	327(26.3%)	583(22.6%)	<0.0001
Rate controlling drugs						
Beta-blockers, n (%)	3482(56.9%)	569(47.9%)	633(56.8%)	722(58%)	1558(60.5%)	<0.0001
Calcium-channel blockers, n (%)	1105(18%)	203(17.1%)	246(22.1%)	216(17.4%)	440(17.1%)	0.1797
Diltiazem, n (%)	174(2.8%)	46(3.9%)	49(4.4%)	29(2.3%)	50(1.9%)	<0.0001
Verapamil, n (%)	73(1.2%)	15(1.3%)	13(1.2%)	20(1.6%)	25(1%)	0.4728
Digoxin, n (%)	553(9%)	226(19%)	130(11.7%)	100(8%)	97(3.8%)	<0.0001
Antidiabetics, n (%)	872(14.2%)	122(10.3%)	146(13.1%)	178(14.3%)	426(16.5%)	<0.0001

* P for trend (Jonckheere -Terpstra test)

Legend: Afib: Atrial fibrillation, BMI: Body Mass Index, VKA: vitamin K antagonist, DOAC: Direct Oral Anticoagulants, AT2-antgonist, Angiotensin II receptor antagonists. CCB: Calcium Channel Blockers.

starting in 2011. Their use was much higher in those with CHA_2DS_2-VASc scores of 1 and ≥2, explained by an 'age effect' since ≥ 75 years old was a central item in the CHA_2DS_2-VASc score [Figure 4].

VKAs *vs.* DOACs

On a semester basis from 2012 to 2019, VKA proportions decreased over time [Figure 5]. On the other hand, we observe an important increase in the use of DOACs starting in the second semester of 2012, reaching its highest proportion of 35% in semester 1 2019.

Cost analysis

The total cost for all patients under VKA treatment in Flanders for 2019 was equal to 440730€/year. We obtained a cost of 885000€ if a simulation of DOAC use was performed for these patients. The incremental DALYs gained per prevented stroke was 803, yielding an incremental cost effectiveness ratio (ICER) of 553 €/DALY of prevented stroke [Table 2]. For *scenario 2*, we considered the incremental cost of switching all anticoagulation-eligible Afib Flemish patients in 2019 to DOACs, including those with a CHA_2DS_2-VASc score of at least 2, while excluding the proportion who had a history of bleeding. The corresponding ICER was 824 €/DALY of prevented stroke [Table 2].

Discussion

Main findings

Afib cases increased over time and within age groups in Flanders, with the highest proportions found in the above 75 years old group. Specifically, the CHA_2DS_2-VASc score ≥ 2 group had the highest proportion, especially for the last five years. Concurrently, an increase in Afib prevalence and incidence over the years was observed in patients older than 65 years old, reaching 14% and 2.6% in 2019 in the above 75 years old, respectively, explained by age being the most important risk factor for Afib in the general population and suggesting an underdiagnosis of Afib in the previous years, as well as the influence of increased awareness of the disease.

Our data show a higher trend of OACs in the first year of Afib diagnosis in the CHA_2DS_2-VASc scores of 1 and ≥ 2 since 2011, explained by the rise in DOAC use and marketing since their injection into the Belgian market. Another reason is the lowered threshold of treatment with OACs due to the introduction of a more sensitive tool, the CHA_2DS_2-VASc score compared to the CHADS2 score.

For comorbidities such as hypertension and bleeding history, DOACs are the agents of choice because of the higher food and drug interactions associated with VKAs, although they require dose adjustment according to renal function. Hypertension and renal dysfunction partially explain the predominance of beta-blockers and Ace inhibitors/AT2 antagonists as co-medications.

Regarding the ICERs calculated, they show to be cost-effective compared to a threshold of 20,000 €/DALY.

Findings in perspective

The worldwide prevalence of AFib in 2017 was estimated at 37.574 million cases (4977 cases per million inhabitants), increasing from 28.533 million cases in 2007 (4255 cases per million inhabitants) and from 22.169 million cases in 1997 (3751 cases per million inhabitants). Which means that the prevalence of AF increased by 17% and 33% compared to 2007 and 1997, respectively. It is expected that by 2060 17,9 million people in Europe will suffer from this condition [19]. In Italy in 2016 The overall prevalence was 7.3% and as high as 16% for the 85 +, comparable to the numbers in Flanders [20]. According to the EurObservational Research Programme (EORP) registry, the proportion of patients ≥ 75 years old significantly increased over time, engendered by two reasons: first, the higher screening of Afib patients, thus explaining the increased prevalence and incidence, and second, the demographic transition accompanied by an enhanced management of cardiovascular diseases [21]. OAC prescription is strongly recommended for those with CHA_2DS_2-VASc scores ≥ 2 in men and ≥ 3 in women [3]. On a national level, the GLORIA registry showed 80.1% use of anticoagulants in Belgium, ranking higher in comparison to other European countries [22].

In comparison with the UK between 2000 and 2016, the proportion of prescribed anticoagulants increased from 35.4% to 75.5% in CHA_2DS_2-VASc ≥ 2, from 32.8% to 47.1% in moderate risk; only did it decrease in low-risk patients from 19.9% to 9.7%, while numbers increased for the three categories in Flanders, but in lower proportions for the moderate and high-risk patients [23]. In Europe specifically, patients aged < 65 years are less frequently prescribed OACs than those aged ≥ 75 years because of bleeding risk concerns; European physicians perceive bleeding risk as a major reason of non-OAC prescription generally [24]. A significant increase in OAC use was reported in the last 10 years, from 67% in EuroHeartSurvey (EHS) to 85% in EORP over the last decade in Europe [21]. Factors associated with OAC prescriptions are 65–75 years old, a BMI ≥ 25 kg/m^2, and creatinine clearance of 30–59 mL/min, and as hypertension, heart failure and previous stroke/TIA are the most prevalent risk factors for thromboembolic complications, they are strongly associated with a greater frequency of OAC prescriptions [24].

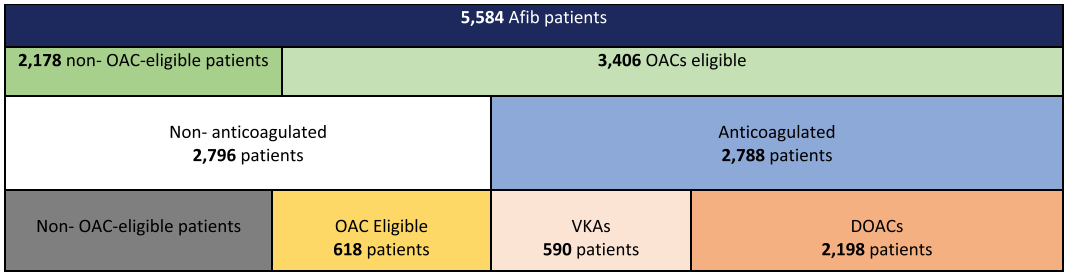

Figure 1. Afib in the INTEGO registry in 2019 stratified by anticoagulation eligibility.

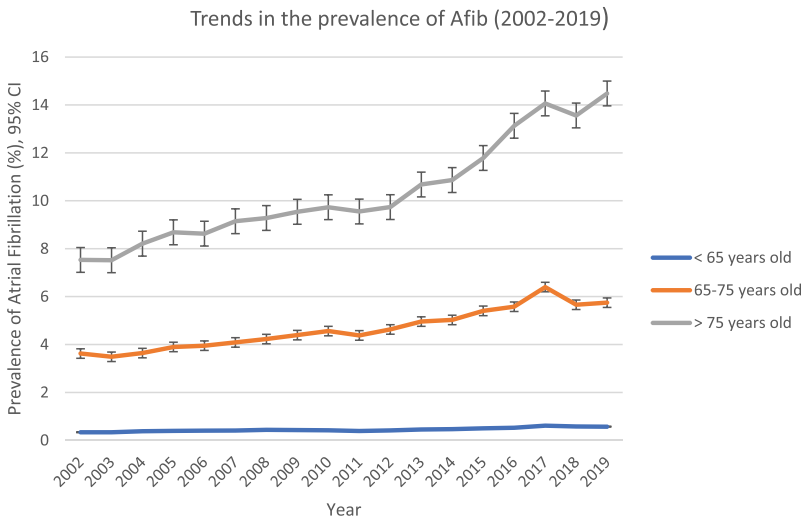

Figure 2. The prevalence of patients with atrial fibrillation in the INTEGO population, in three age groups (2002–2019).

In the Belgian GLORIA registry, 14.5% were on VKAs and 65.6% were on DOACs up to 2018, higher than our results in Flanders between 2015 and 2019 [22]. In comparison with our results, the numbers in the worldwide GLORIA-AF registry ranked higher: 83.8% were prescribed OACs among multimorbid cases, of which 60.2% were prescribed DOACs and 23.6% were prescribed VKAs between 2014 and 2016. The rate of prescription of antiplatelets was 25.9% in our study, significantly higher as compared to the GLORIA-AF (11%) and the EORP-AF (19.8%) registries [24,25].*** [26] In the GARFIELD-AF registry, 51.4% of DOACs and 48.6% of VKAs were prescribed up to 2016, higher than our numbers, with fewer discrepancies between the two OAC types [8]. The most common chronic comorbidities were hypertension, coronary disease and heart failure in the European Society of Cardiology (ESC-AF) registry [9]. Patients with multimorbidity-prescribed DOACs, agents of choice in polypharmacy cases, are more likely to have paroxysmal Afib and have fewer comorbidities than those prescribed VKAs. Factors associated with prescriptions for VKA use in multimorbid AFib patients appear to be: age <75, myocardial infarction, congestive heart failure, diabetes, MI, congestive HF, diabetes mellitus, mellitus and creatinine clearance < 60 mL/min [24].

In Europe, stroke is the second most common cause of death and a leading cause of adult disability. Conversely, the declining trends in mortality and lost DALYs between 1990 and 2017 are expected to continue until 2047 [27]. A shift in stroke mortality to stroke morbidity is likely to be seen in the coming years for two reasons: less severe stroke episodes due to primary prevention implementation and better care of patients received in both the acute and long-term stages of stroke. The highest burden of DALYs in 2017 was seen in countries with a high sociodemographic index [19]. By itself, the ICER does not allow policymakers to draw conclusions about the efficiency of an intervention; a threshold value is required, beyond which the intervention is not considered profitable [28]. Because our results were calculated in terms of €/DALY, it is worth noting the difference between the two quality of life measurement tools. The number of DALYs of a disease reflects the number of healthy life-years lost in a population due to the disease. In cost-utility analyses, health outcomes are frequently expressed in QALYs, a measure where the years of life gained through intervention are weighted by the health-related quality of life during these years. In our case, a prevented DALY is the equivalent of a gained QALY [27]. As decision-making on the ICER threshold in Belgium

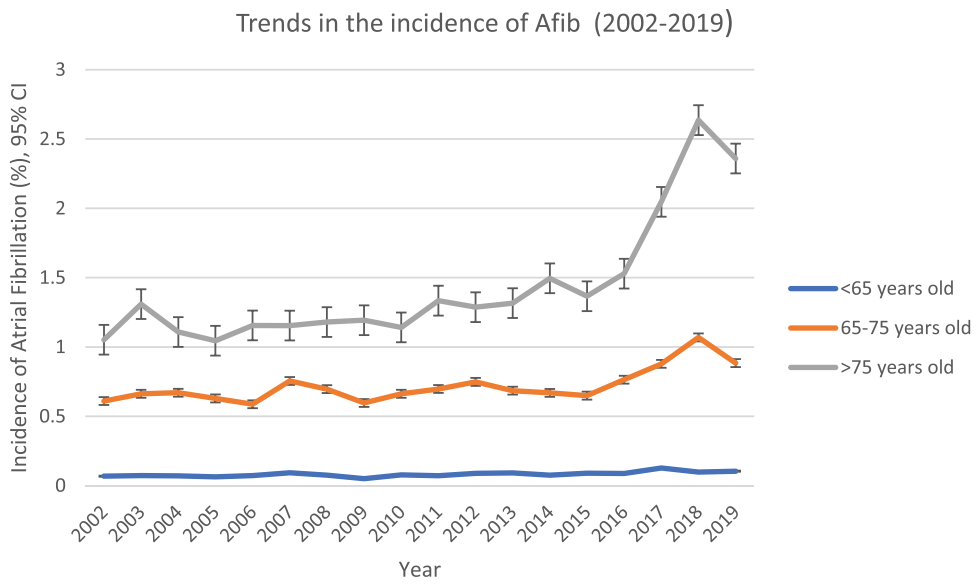

Figure 3. The incidence of patients with atrial fibrillation in the INTEGO population, in three age groups (2002–2019).

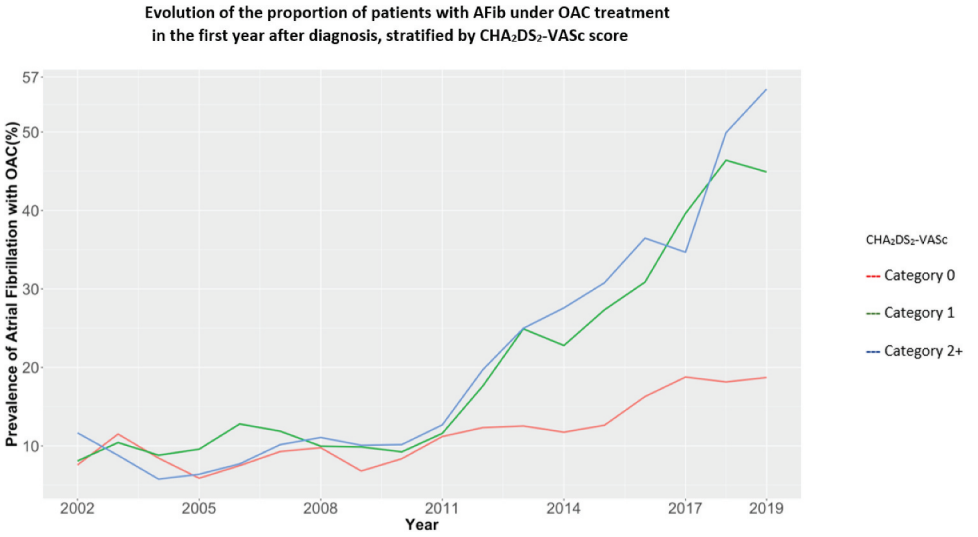

Figure 4. Trends in OAC treatment stratified by CHA_2DS_2-VASc score.

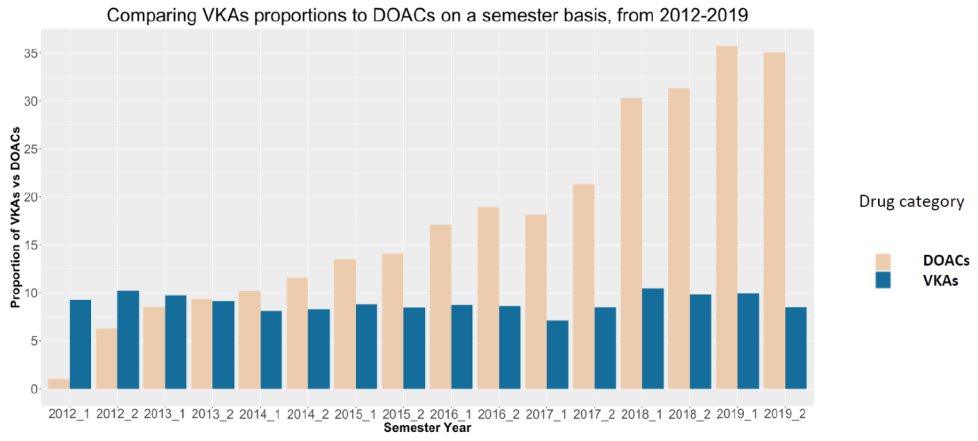

Figure 5. Vitamin K antagonists (VKAs) vs Direct Anticoagulants (DOACS) on a semester basis, from 2012–2019.

Table 2. Cost-utility analysis in Flanders, 2019.

Scenario 1	**590** VKA	→	DOAC
Δ cost (€)		444,270 €	
Prevented strokes		13 [9.7–21.5]	
Δ DALYs gained		803	
ICER (€/DALY of prevented stroke)		**553**	
Scenario 2	**3,406** OAC eligible	→	DOAC
Δ cost (€)		1,371,270 €	
Prevented strokes		26 [19–42.6]	
Δ DALYs gained		1,664	
ICER (€/DALY of prevented stroke)		**824**	

Legend: DALY: Disability Adjusted Life Years, ICER: Incremental Cost Effectiveness Ratio, VKA: vitamin K antagonists, DOAC: Direct Anticoagulants, OAC: Oral anticoagulants.

remains an interactive deliberation process, a threshold of 20000€/QALY was used as a reference. For both *scenarios*, they are cost-effective since they are below 20000€/QALY. In comparison with a cost-effectiveness study on dabigatran, the latter was shown to be highly cost-effective when compared to real-world Belgian-based INR-control clinical practice warfarin treatment. An additional cost taken into consideration in comparison with our study was the clinical event hospitalization costs [7].

Strengths

This study offers a comprehensive and updated overview of longitudinal information in Flanders since 2002 to 2019. It is specific to Flanders and combines an Afib descriptive epidemiologic part and a cost-utility analysis for all DOACs combined. Additionally, it is the first study in Belgium accounting for a NNSw offering simulation scenarios of contemporary real cost-utility benefits of switching patients from VKAS to DOACs in 2019.

Limitations

The numbers we have are restricted to the ambulatory practice setting, thus lacking hospitalized patients. The method used to calculate the YLL is subject to two points of discussion: the first is the standardization of the YLL at a national level without accounting for internal disparities, and the second is the correction of YLL for the comorbidities of the deceased, both interfering with the estimation of the YLL [28]. Also, the competing risk analysis is not taken into consideration; multimorbidity, which is common in the older population, has a high impact on mortality. Additionally, the NNSw and NNT retrieved from the systematic reviews do not exactly conform to the Flemish population in terms of comorbidities and age, and the NNT is based on the comparison between Apixaban and Aspirin groups, limiting an exact extrapolation of the RR. Additionally, we assumed that the risk follows a proportional speed trend, allowing us to proportionally convert the NNSw from 1.7 to a 1-year period. Furthermore, the DOAC costs and the number of yearly GP visits for INR monitoring are only averages, making our results estimations. Finally, the lack of an ICER threshold in Belgium bound our interpretations of assumptions, and the variability of health care systems around the world makes it difficult to generalize our results to other countries.

Future implications

Switching to DOACs has been shown to be beneficial and cost-effective. Still, there remains enormous potential in looking at patients from their multimorbidity perspective to better assess their prognosis. Demographic transition is a major cause of the European Union prevalence increase, and we would be interested in exploring OAC prescription trends will be impacted by the parallel rise in awareness about Afib screening and enhanced management. With respect to the cost-effectiveness side, future roads worth exploring are the effects of different ICER thresholds and the introduction of DOAC generics into the market.

Conclusion

This registry-based study showed a significant positive trend in prevalence and incidence of non-valvular Afib accompanied by an increase in OAC use in Flanders between 2002 and 2019, with an important overtaking of DOACs since 2014. Switching VKA users to DOACs and prescribing DOACs to eligible patients are both cost-effective compared to a threshold of 20000€/DALY.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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