UCLouvain

Faculté de Santé Publique

The impact of switching patients with non-valvular Afib from warfarin to DOACs in terms of the burden caused by the complications of the disease

L'impact en termes de fardeau des complications de la maladie de fibrillation auriculaire non-valvulaire après commutation des patients sous AVKs aux AODs

Mémoire réalisé par : Elvire Nakhoul
Promoteur : Professeur Jean-Marie Degryse
Co-promoteur : Professeur Bert Vaes

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Abstract

Context

With the simultaneous presence of Vitamin K Antagonists (VKAs) and Direct Oral Anticoagulants (DOACs) as anticoagulants in the Belgian market for the treatment of Atrial Fibrillation (Afib), there has been an evolution in the prescription behavior since the introduction of the newer agents, as well as an impact on stroke prevention.

Aim

The aim is to explore the prescription behavior of oral anticoagulants (OACs) as well as the prevalence and incidence of Afib in the Belgian setting from 2002 to 2019 based on the integrated computerized network (INTEGO) database, while also exploring the impact of switching patients with non-valvular Afib from VKAs to DOACs in terms of the burden caused by stroke as a complication of the disease.

Methods

Data were obtained from INTEGO, a Flemish general practice-based morbidity registration network. Inclusion criteria were at least one GP contact between 2002 and 2019, including yearly prevalent and incident chronic Afib cases, with at least 1 year follow-up. Both OAC classes were included, and drugs and laboratory tests costs were retrieved respectively from the Belgian Centre for Pharmacotherapeutic Information (BCFI) and INAMI sites, based on the 2019 public prices. The number of DALYs was based on the Global Burden of Disease (GBD) literature. The CHA2DS2-VASc score was used as stroke risk stratification tool at time of diagnosis. We conducted cost-utility analyses for 2012-2019 accounting for the global benefit, in terms of (cost of prevented stroke / DALY), of switching above 65-year-old patients in Flanders under VKAs to DOACs, based on the real 2019 numbers in a *first scenario*, and the results if all anticoagulation eligible Afib patients in Flanders were switched to DOACs in *scenario 2*. We calculated a Number Needed to Switch (NNSw) to estimate the number of prevented strokes per year.

Results

Total population with Afib consisted of 8508 patients. An important increase is perceptible in both prevalence and incidence among the above 75 years old. A striking increase of OACS use is observed in CHA2DS2- VASc scores of 1 and at least 2, simultaneously with an overtaking in the use of DOACs starting the second semester of the year 2012 compared to VKAs. The incremental cost effectiveness ratio (ICER) of *scenario 1* was 647 €/DALY of prevented stroke and 1,167 €/DALY of prevented stroke for *scenario 2*.

Conclusion

In this registry-based study, we found a significant positive trend in OAC and DOACs use in Flanders between 2002 and 2019, as well as an increasing prevalence and incidence in above 75 years-old specifically. *Scenarios 1* and *2* are cost-effective when compared to a threshold of 20 000 €/DALY.

Abstrait

Contexte

Avec la présence simultanée d'antagonistes de la vitamine K (AVK) et d'anticoagulants oraux directs (AOD) comme anticoagulants sur le marché belge pour le traitement de la fibrillation auriculaire (FA), il y a eu une évolution dans le comportement de prescription depuis l'introduction des nouveaux agents, ainsi qu'un impact sur la prévention des accidents vasculaires cérébraux (AVC).

Objectif

L'objectif est d'explorer le comportement de prescription des anticoagulants oraux (ACO) ainsi que la prévalence et l'incidence de la FA dans le contexte belge de 2002 à 2019, au travers de la base de données *integrated computerized network* (INTEGO), tout en explorant également l'impact de commutation des patients souffrant de FA non- valvulaire des AVK aux AOD, en termes du fardeau causé par les accidents vasculaires cérébraux (AVC) en tant que complication de la maladie.

Méthodes

Les données ont été obtenues auprès de INTEGO, un réseau flamand d'enregistrement de la morbidité de la médecine générale. Les critères d'inclusion étaient au moins un contact avec un médecin généraliste entre 2002 et 2019, y compris les cas chroniques prévalents annuels de AF ainsi que les nouveaux, avec au moins un an de suivi. Les deux classes d'ACO ont été incluses, et les coûts des médicaments et des tests de laboratoire ont été récupérés respectivement sur les sites du Centre belge d'information pharmacothérapeutique (BCFI) et de l'INAMI, sur la base des prix publics de 2019. Le nombre de DALY fut basé sur la littérature mondiale du fardeau de la maladie. Le score CHA2DS2-VASc a été utilisé comme outil de stratification du risque d'AVC au moment du diagnostic. Nous avons effectué des analyses coût-utilité pour 2012-2019 en tenant compte du bénéfice global, en termes de coût de l'AVC évité / DALY, de la commutation des patients flamands âgés d'au moins 65 ans sous AVK passés aux AOD sur base des chiffres de 2019 dans un premier scénario, la simulation de la commutation de cette catégorie de patients sous ACO vers des AVK comme second cas, et enfin les résultats de prescription d'AOD à tous les patients souffrant de FA, éligibles à l'anticoagulation et âgés de plus de 65 ans en Flandres. Nous avons calculé un *Number Needed to Switch* (NNSw) afin d'obtenir le nombre d'AVC évités par an.

Résultats

La population totale souffrant de FA est composée de 8508 patients. Une augmentation importante est perceptible à la fois pour la prévalence et l'incidence chez les âgés de plus de 75 ans. Une augmentation frappante de l'utilisation des ACOs est observée pour les scores CHA2DS2-VASc de 1 et au moins 2, parallèlement à un dépassement de l'utilisation des AODs à partir du deuxième semestre de l'année 2012 par rapport aux AVK. Le rapport coût-efficacité différentiel (*ICER*) du *scénario 1* était de 647 € / DALY d'AVC évité et de 1,167 € / DALY d'AVC évité pour le *scénario 2*.

Conclusion

Dans cette étude, nous avons trouvé une tendance significativement positive pour l'utilisation des ACO et des AOD en Flandres entre 2002 et 2019, ainsi qu'une augmentation de la prévalence et de l'incidence chez les personnes âgées de plus de 75 ans en particulier. Les *scénarios 1* et *2* sont rentables par rapport à un seuil de 20 000 € / DALY.

Introduction

Atrial fibrillation (Afib) is a type of heart arrythmia identified by rapid, uncoordinated electrical impulses in the atrium, with a prevalence in the general population appraising to 2% (January et al. 2019; Kakkar et al. 2012). Afib is divided into valvular and non-valvular Afib (NVAF). The former pertains to rheumatic valvular disease or mechanical heart valve (Kirchhof et al. 2016). Among the burdensome complications of Afib are ischemic strokes, which risk is assessed by the CHAD2DS2-VASc risk stratification score (January et al. 2019). The European Society of Cardiology (ESC) guidelines have recommended oral anticoagulants (OACs) as a treatment of choice for Afib, with a conclusive evidence of their use in a CHAD2DS2-VASc score of at least 1 for men and 2 for women (Kirchhof et al. 2016). The first OACs were the vitamin K antagonists (VKAs), particularly warfarin. They require frequent hemostatic parameters monitoring because of their narrow therapeutic range, unlike the direct oral anticoagulants (DOACs) which are characterized by their predictable efficacy and reduced need for monitoring (Kirchhof et al. 2016).

Compared to warfarin, DOACs showed to significantly reduce the risk of stroke or systemic embolism, all cause-mortality and intracranial hemorrhage but to increase the risk of gastrointestinal bleeding on another hand (de Souza Lima Bitar et al. 2019; Ruff et al. 2014). Two out of the three cost-effectiveness analyses that have been conducted in Belgium concluded that Rivaroxaban and Dabigatran were cost-effective alternatives for VKAs for stroke and systemic embolism prevention (Kleintjens et al. 2013; Wouters et al. 2013). As for Afib registries, the worldwide prospective ongoing GARFIELD-AF showed that 48.6% of newly Afib diagnosed patients received a VKA as a first treatment between 2013 and 2016 (Haas et al. 2019). Also, in the European EORP-AF registry, the proportion of VKAs was 71.6% out of the 80% anticoagulated patients till March 2013 (Lip et al. 2015). In Belgium, DOACs have gained a tremendous increase of use since their introduction in the market in 2012 (Van Brabandt et al. 2017). Until 2017, up to 50% of Belgian patients were still under VKA treatment (INAMI 2017).

In 2016, stroke ranked second cause of global DALYs in the world. The rate of years of life lost (YLL) due to stroke tremendously increased with age compared to the years lived with disability (YLD), especially in old adults (GBD 2016 Stroke Collaborators, 2019). 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 from VKAs to DOACs in terms of cost per DALY of prevented stroke. This raises the question on what is the benefit of switching above 65-year-old patients in Flanders from VKAs to DOACs, in terms of cost per DALY of prevented stroke, between the years 2012-2019?

The integrated computerized network (INTEGO) is a unique Flemish computerized morbidity registration network at the Department of General Practice of the University of Leuven in Belgium. Information is retrieved from electronic health records registered prospectively and routinely by general practitioner doctors evenly spread over Flanders, allowing for longitudinal analyses conduction. Data includes patient information including age and gender, history of diseases, drug prescriptions and laboratory test results (Truyers et al. 2014).

We aim to first study the pattern of OACs prescriptions in Flanders based on the INTEGO database from 2002-2019, before conducting a cost-utility analysis in terms of the potential benefit, in terms of DALYs, of switching above 65-year-old NVAF patients from warfarin to DOACs.

Methods

Data collection

Data was collected from the INTEGO database, which gathers information from the medical electronic health record software system, allowing general practitioners to enter coded information routinely (Truyers et al. 2014). Data is centrally stored at the department of general practice at KU Leuven University in Belgium. The recorded information is 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. All one hundred eleven participating doctors, evenly spread over seventy-nine practices in Flanders, must meet the INTEGO eligibility criteria to participate. The database includes more than 200 000 patients; studies have shown that they are representative of the Flemish population in terms of age and sex (Truyers et al. 2014).

Drugs and laboratory tests costs were retrieved respectively from the Belgian Centre for Pharmacotherapeutic Information (BCFI) and INAMI sites, based on the 2019 public prices. The number of DALYs used to quantify the burden caused by a stroke was based on the Global Burden of Disease literature (GBD 2017 DALYs and HALE Collaborators, 2018).

Patient selection

For the descriptive part of our study, we are interested to gather all patients diagnosed with chronic Afib in Flanders between 2002-2019, including yearly prevalent and incident cases. Comprised patients were those who had at least one visit to their GP per year, between 2002 and 2019. Among the newly Afib diagnosed patients (ICPC-2 code K78), eligible ones were those who had a follow-up of at least 1 year after the diagnosis, accounting for the necessary time to start oral anticoagulation therapy.

For the cost-utility analyses, included patients were the prevalent above 65 years Afib cases diagnosed earlier. From those, we are interested specifically in patients under OACs, and particularly VKAs.

Background variables

Patients diagnosed with Afib were divided into three categories, according to their ages: those who were below 65 years old, those between 65-75 years old and finally those > 75 years old. Females' Afib proportion was also considered, and patients' average BMI was calculated.

Co-morbidities were retrieved based on the predisposing conditions needed to calculate the $CHAD_2DS_2$-VASc and HAS-BLED scores at time of Afib diagnosis. These variables include the following: congestive heart failure/ left ventricular dysfunction (ICPC-2 code K77; 1 point), history of hypertension (ICPC-2 code K86, K87; 1 point), diabetes (ICPC-2 code T89, T90; 1 point), history of thromboembolic event, whether transient ischemic attack (TIA) or stroke (ICPC-2 code K89, K90; 2 points) and history of vascular disease, whether acute myocardial infarction or peripheral artery disease (PAD) (ICPC-2 code K75, K93; 1 point). For females, an additional point was added, as well as for people aged 65-74 years old, and two points for above 75 years old. $CHAD_2DS_2$-VASc scores were divided into three categories: category 0, category 1, and category ≥ 2.

Among the bleeding risk scores developed, the HAS-BLED score was used to assess one-year risk of major bleeding in patients with atrial fibrillation. Its variables include hypertension (1 point), renal function (eGFR<60 ml/min) (1 point), stroke (1 point), bleeding history/ predisposition (1 point), labile INR (1 point), age > 65 years old (1 point) and drug/ alcohol consumption (1 point).

Treatment

Oral anticoagulants prescriptions

Included VKAs were warfarin (ATC code B01AA03), phenprocoumon (ATC code B01AA04) and acenocoumarol (ATC code B01AA07). Regarding DOACs, four of these medications are reimbursed in Belgium for the present moment: apixaban (ATC code B01AF02), dabigatran etexilate (ATC code B01AE07), rivaroxaban (ATC code B01AF01) and edoxaban (ATC code B01AF03).

Co-medications prescriptions

The prescription of a comedication was considered if the patient had at least two prescriptions in a year. Cardiovascular medications included antiplatelet agents (ATC code B01AC), angiotensin converting-enzyme (ACE) inhibitors (ATC codes C09A and C09B), angiotensin II (ATII) antagonists (ATC codes C09A, C09B, C09C, C09D and C09X), diuretics (ATC code C03) and dihydropyridine (ATC code C08CA). Other cardiovascular medications prescribed in AF were recorded and included all class I antiarrhythmic drugs (ATC codes C01BA, C01BB, C01BC, C01BG), including amiodarone (ATC code C01BD01), and rate controlling drugs: beta-blockers (ATC codes C07AA and C07AB), calcium-channel blockers (ATC codes C08CA, C08DA, C08DB, C08EA), including diltiazem (ATC code C08DB01) and

verapamil (ATC code C08DA01), and finally digoxin (ATC code C01AA). Drugs used in diabetes were also recorded (ATC code A10).

Model Structure and Outcomes

Since DOACs have been introduced into the Belgian market in 2012, we conducted cost-utility analyses for 2012-2019 based on two chosen scenarios. 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, based on the real 2019 number of patients under VKAs. The *second scenario* assumes the global benefit, in terms of (cost / DALY), if all eligible above 65-year-old Afib patients in Flanders were prescribed DOACs. For the latter model, as the dual increase in bleeding and thrombotic risk in the elderly lead to uncertainty in the prescription of anticoagulants, we only included patients with a $CHAD_2DS_2$-VASc score of 2 (70%) and excluded the 15% of them who have a bleeding history (table 1).

In order to proceed with the cost-utility analysis, we need both an incremental cost and an incremental utility in terms of DALYs. For the latter, the Number Needed to Switch (NNSw) was calculated based on data produced by a systematic review of Caldeira et al "Non-Vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis" from the Journal of *Archives of Gerontology and Geriatrics* (2019). The first step relied on retrieving the Absolute Risk Reduction from the Relative Risk of stroke and systemic embolism of DOACs compared to VKAs in the above 75 years old group. From there, we were able to calculate the NNSw based on the following formula: $\text{NNSw} = \frac{1}{ARR}$. A corresponding absolute risk reduction of 0.012 was obtained from a Relative Risk of 0.71 in ≥ 75 years old patients, leading to a NNSw of 85 patients in 1.8 years, which is equivalent to 47 patients in 1 year [62.5- 140] (appendix 1). Based on the Intego data, we retrieved the number of VKA users in Flanders for 2019 for *scenario 1*, and the number of anticoagulation eligible patients for *scenario 2*. From there, we divided these numbers by the NNSw to get the number of prevented strokes per year in each case. Regarding the confidence interval calculation around the prevented strokes, it was calculated based on proportions where the number of prevented strokes constitutes the numerator among patients > 65 years old in Flanders under VKAs in 2019 for *scenario 1*, while the denominator of *scenario 2* are patients > 65 years old with Afib in Flanders in 2019. Knowing that the burden of ischemic stroke is 55 DALYs/ person in accordance with the GBD study of 2017, we can calculate the incremental DALYs by multiplying the burden of ischemic stroke in DALYs/person by the number of prevented strokes per year in Flanders for 2019 for each scenario (appendix 2).

As for the incremental cost, it was based on the 2019 public prices in the Belgian market. The total cost of 747€ of VKA/ person/year included the cost of the drug in addition to the yearly blood monitoring, which combines the cost of INR and 15 yearly GP visits on average, according to the Inter Mutualistic Agency (IMA). As for the mean cost of DOACs, it accounted for the average cost of a DOAC/person/year based on the average doses per patient, yielding 1500 €/person/year (appendix 2).

Statistical Analysis

The baseline characteristics of patients with prevalent Afib in the registry were compared over four, five-year periods. 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 8508 between 2002 and 2019 and has increased from 1100 between 2002 and 2006 to 4234 cases in the last five years. The prevalence of patients with Afib increased with age, with the highest proportions lying in the above 75 years old group, reaching its highest of 51.6% between 2015 and 2019 ($p<0.0001$). Less than half of patients are women, in a range of 45%, but results are non-significant. The highest prevalence of 69.7% was in the CHAD2DS2-VASc ≥ 2 score group, reaching its highest of 72.5% between 2015-2019 ($p<0.0001$). The overall score was significantly higher compared to 11.9% in each of the two other groups. Patients' BMI were in the overweight range across the years (27.3 ± 4.1). As for co-morbidities, we perceive that a history of hypertension is the most common condition in up to 27% of Afib patients between 2011 and 2015 ($p= 0.6395$), with the second most common condition being bleeding history (15.3%, $p=0.699$), followed by renal/liver dysfunction (14.1%, $p<0.0001$), diabetes (12%, $p=0.2773$), history of thromboembolic events (10.3%, $p=0.3456$), vascular disease (7.2%, $p= 0.2769$) and heart failure (5.1%, $p= 0.5001$). Specifically, renal dysfunction was more likely seen since 2011 compared to the previous years, reaching a proportion of 17% ($p<0.0001$). Regarding Afib patients under OACs treatment, we observe an increase of VKA use to 30% between 2007 and 2011, before decreasing since the introduction of DOACs in the Belgian market in 2012 to reach 8.6% between 2015 and 2019 ($p<0.0001$). In parallel, an important increase in DOACs have been detected since 2011, reaching 43.1% between 2015 and 2019. Finally, on the level of cardiovascular medications, we notice that beta-blockers are the most widely used drugs among Afib patients, up to 56.7% between 2015 and 2019,

followed by Ace inhibitors/AT2 antagonists (30.3%, p<0.0001) and antiplatelet agents (25.9%, p= 0.8311) (table 1).

Table 1. Baseline characteristics of patients with Afib

Variables	All patients	2002- 2006	2007-2011	2011-2015	2015-2019	P*
Patients with AF	8508	1100	1275	1899	4234	
Baseline Characteristics						
Age of patients						
< 65 y.o., n (%)	2034(23.9%)	323(29.4%)	376(29.5%)	467(24.6%)	868(20.5%)	<0.0001
65-75 y.o., n (%)	2619(30.8%)	400(36.4%)	423(33.2%)	613(32.3%)	1183(27.9%)	<0.0001
> 75 y.o., n (%)	3855(45.3%)	377(34.3%)	476(37.3%)	819(43.1%)	2183(51.6%)	<0.0001
Females, n (%)	3880(45.6%)	490(44.5%)	558(43.8%)	882(46.4%)	1950(46.1%)	0.1825
CHAD2DS2-VASc score at time of diagnosis						
Category 0, n (%)	1012(11.9%)	161(14.6%)	196(15.4%)	208(11%)	447(10.6%)	<0.0001
Category 1, n (%)	1562(11.9%)	221(14.6%)	253(15.4%)	371(11%)	717(10.6%)	0.0022
Category ≥2, n (%)	5934(69.7%)	718(65.3%)	826(64.8%)	1320(69.5%)	3070(72.5%)	<0.0001
Patients' BMI	27.3(4.1)	28.2(4.6)	27.6(3.6)	26.9(3.6)	27.3(4.2)	No test available
Co-morbidities						
Heart Failure, n (%)	434(5.1%)	59(5.4%)	66(5.2%)	101(5.3%)	208(4.9%)	0.5001
History of Hypertension, n (%)	2201(25.9%)	272(24.7%)	348(27.3%)	513(27%)	1068(25.2%)	0.6395
Diabetes, n (%)	1020(12%)	121(11%)	142(11.1%)	247(13%)	510(12%)	0.2773
History of thromboembolic event (stroke/TIA), n (%)	880(10.3%)	106(9.6%)	125(9.8%)	205(10.8%)	444(10.5%)	0.3456
Vascular disease (history of Myocardial Infarction or Peripheral Artery Disease), n (%)	616(7.2%)	86(7.8%)	105(8.2%)	121(6.4%)	304(7.2%)	0.2769
Renal/Liver dysfunction, n (%)	1199(14.1%)	11(1%)	139(10.9%)	329(17.3%)	720(17%)	<0.0001
Bleeding history, n (%)	1298(15.3%)	172(15.6%)	193(15.1%)	294(15.5%)	639(15.1%)	0.699
Drug/Alcohol Consumption, n (%)	217(2.6%)	16(1.5%)	21(1.6%)	53(2.8%)	127(3%)	0.0005
Patients' treatment						
VKA, n (%)	1480(17.4%)	276(25.1%)	383(30%)	456(24%)	365(8.6%)	<0.0001
DOAC, n (%)	2245(26.4%)	0(0%)	0(0%)	420(22.1%)	1825(43.1%)	No test available
Cardiovascular medication						
Antiplatelet agents, n (%)	2200(25.9%)	264(24%)	384(30.1%)	453(23.9%)	1099(26%)	0.8311
Ace inhibitors/AT2 antagonists, n (%)	2575(30.3%)	217(19.7%)	301(23.6%)	495(26.1%)	1562(36.9%)	<0.0001
Diuretics, n (%)	1943(22.8%)	189(17.2%)	238(18.7%)	345(18.2%)	1171(27.7%)	<0.0001
Dihydropyridine, n (%)	858(10.1%)	77(7%)	89(7%)	151(8%)	541(12.8%)	<0.0001
Antiarrhythmic drugs, n (%)	1791(21.1%)	224(20.4%)	265(20.8%)	378(19.9%)	924(21.8%)	0.2053
Rate controlling drugs						
Beta-blockers, n (%)	3981(46.8%)	324(29.5%)	473(37.1%)	783(41.2%)	2401(56.7%)	<0.0001
Calcium-channel blockers, n (%)	1082(12.7%)	104(9.5%)	129(10.1%)	194(10.2%)	655(15.5%)	<0.0001
Diltiazem, n (%)	176(2.1%)	23(2.1%)	39(3.1%)	30(1.6%)	84(2%)	0.2369

Verapamil, n (%)	81(1%)	6(0.5%)	6(0.5%)	17(0.9%)	52(1.2%)	0.0054
Digoxin, n (%)	446(5.2%)	130(11.8%)	78(6.1%)	88(4.6%)	150(3.5%)	<0.0001
Antidiabetics, n (%)	871(10.2%)	64(5.8%)	64(5%)	153(8.1%)	590(13.9%)	<0.0001

*** P for trend (Jonckheere -Terpstra test)**

Incidence and Prevalence of Afib

The prevalence graph displays a striking increase of prevalence over time. Between 2002 and 2019, an approximate stagnation in the prevalence of Afib in patients less than 65 years old is perceived, while an increase of prevalence along the years is observed in patients between 65 and 75 years old, with only a slight decrease in 2017. As for the above 75 years old group, an important increase in the last five years is detectable, reaching up a level of 13% approximately in 2019 (figure 1).

As for the incidence rate, it is the lowest in the less than 65 years old group and shows a stable rate along the years, with the highest incidence in the above 75 years old patients' group. However, we see an important decrease in the year 2017 from 2.2% to 1.2%, also noticeable in the 65 to 75 years old patients' group (figure 2). The reason of this decrease is the loss to follow some patients because of the start of use of patients' security number instead of Intego internal codes, starting 2017.

Figure 1. Prevalence of patients with Afib

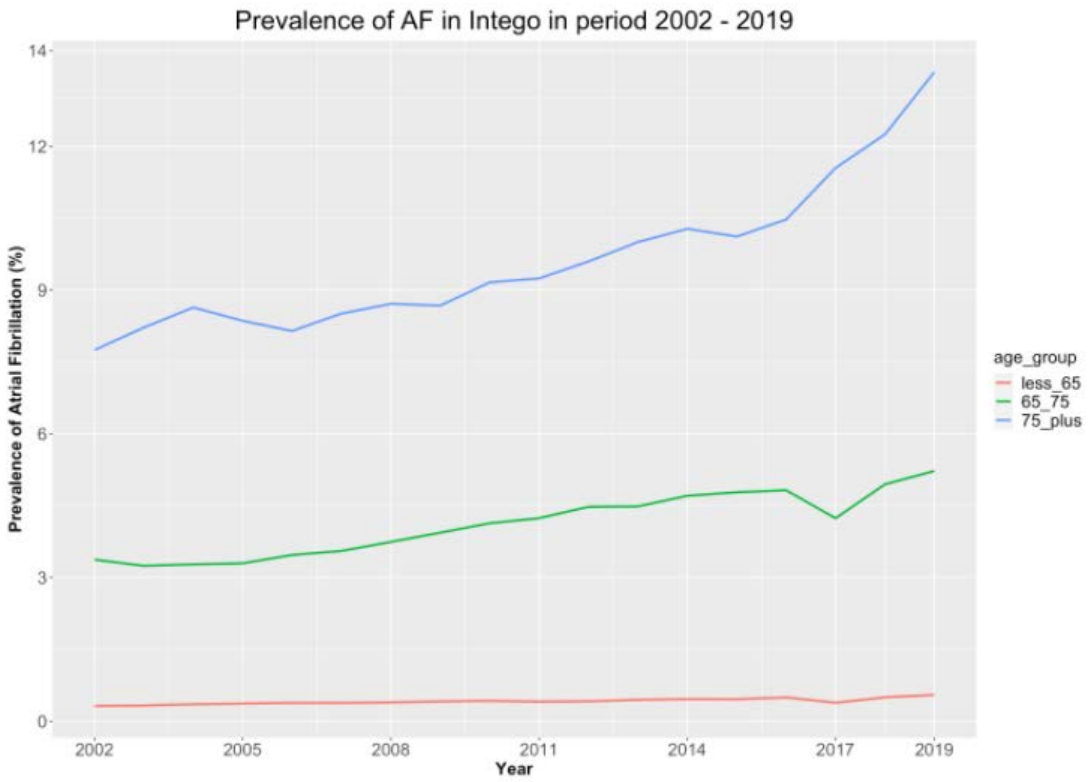
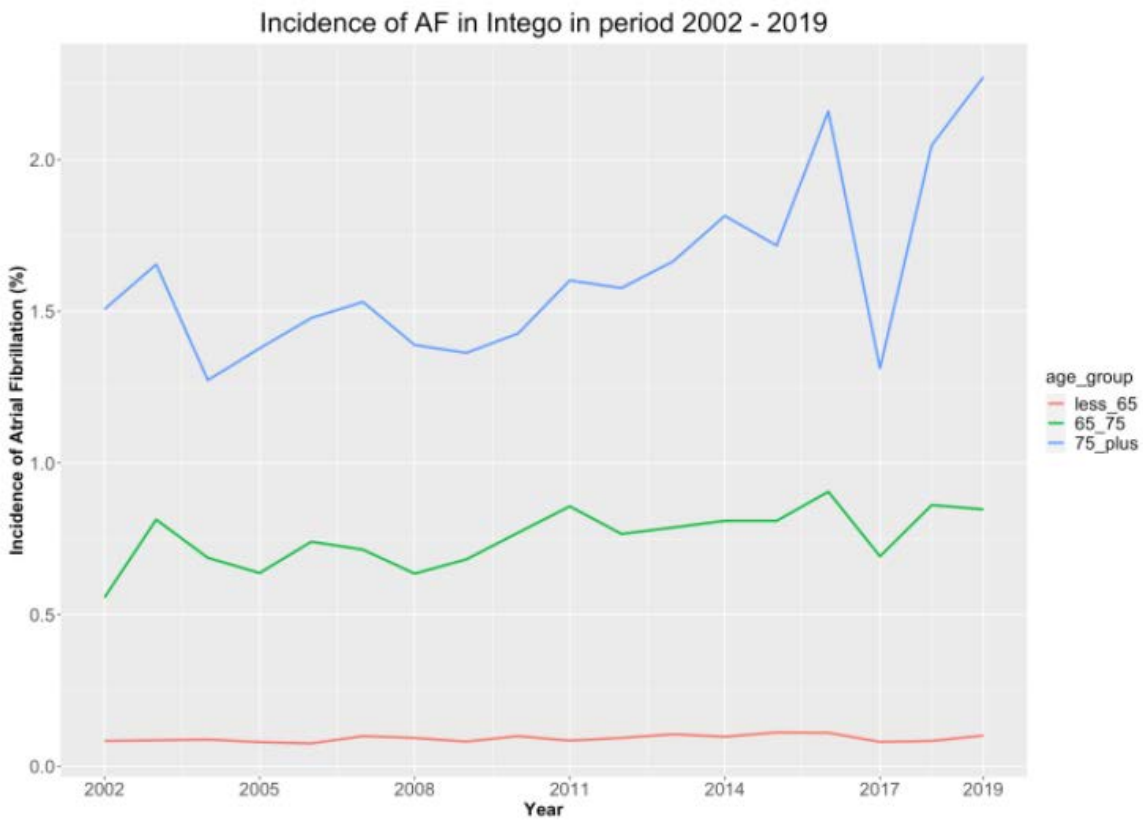


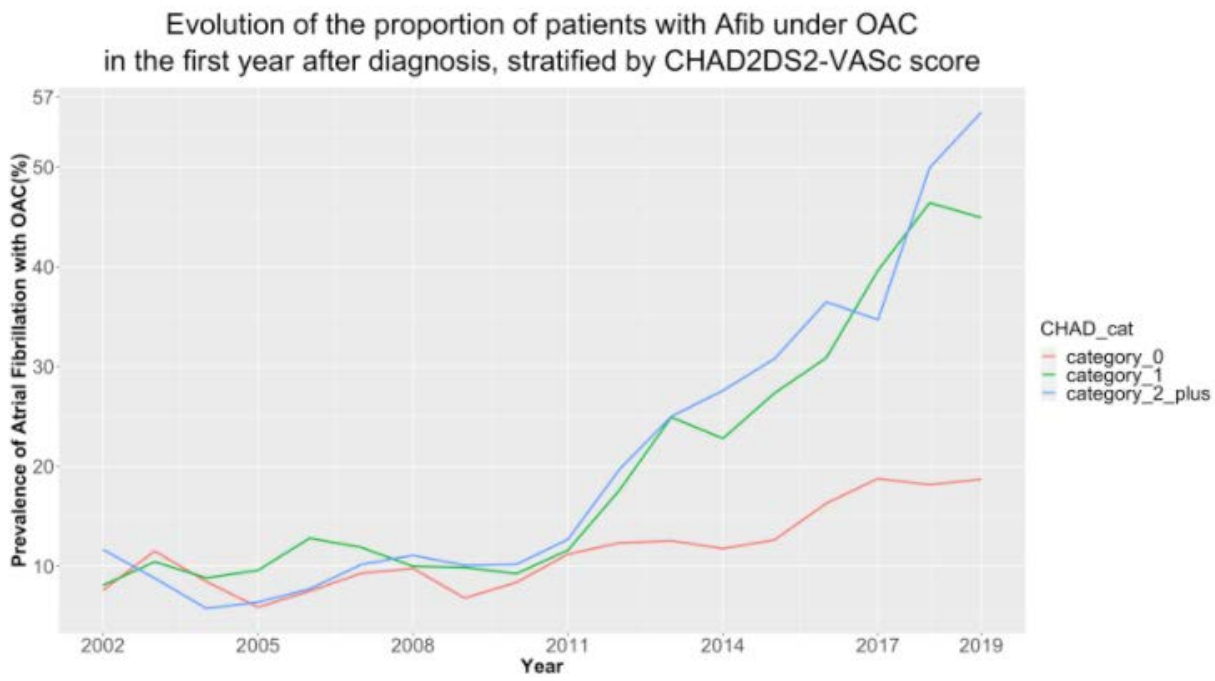
Figure 2. Incidence of patients with Afib



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 starting the year 2011. The use of the OACs is much higher in the CHAD2DS2-VASc scores of 1 and ≥2, with up to 56% of use in the latter group in 2019, explained by an "age effect" since >75 years-old is a central item in the CHAD2DS2-VASc score (figure 3).

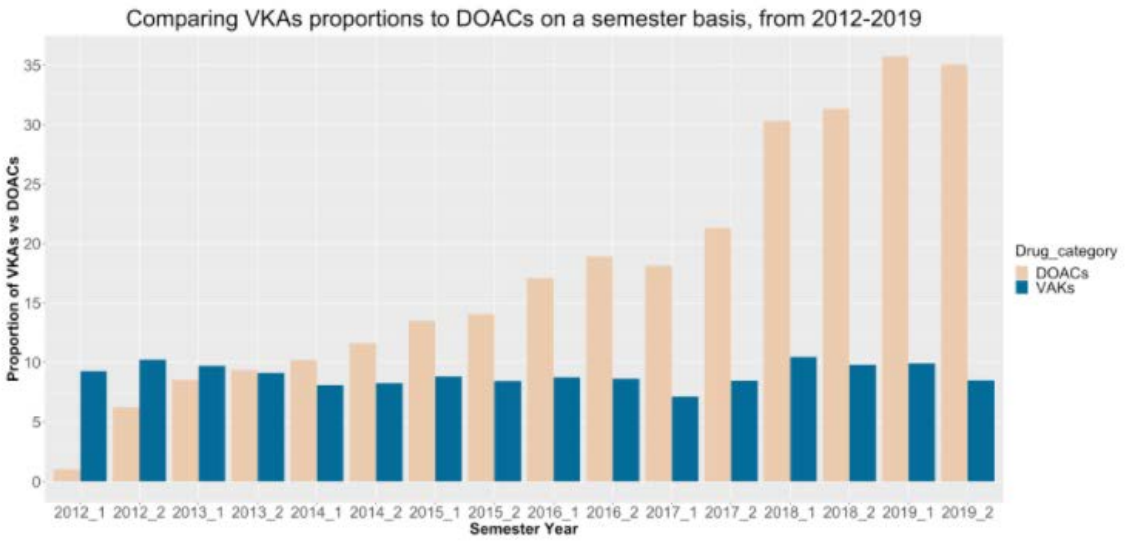
Figure 3. Evolution of patients with Afib under OACS stratified by CHAD2DS2-VASc score



VKAs vs DOACs

When comparing VKAs proportion to DOACs on a semester basis from 2012 to 2019, we notice a virtually constant use of VKAs between 2012 and 2013. On the other hand, we observe an important increase in the use of DOACs starting the second semester of the year 2012. DOACs use constantly increased until the second semester of 2016, later showing a slight decrease in the first semester of the year 2017, to increment again starting semester 1 of 2018 and reaching its highest proportion of 35% in semester 1 of 2019. On another hand, VKAs proportions remain constant at around 10% along the years, with a decrease to a level of 7% in semester 1 of 2017 similarly to DOACs (figure 4). Consequently, the evolution of the proportion of patients with Afib receiving any OAC is mainly due to an increase of DOAC from one side, and to an increased awareness caused by the marketing for DOACs.

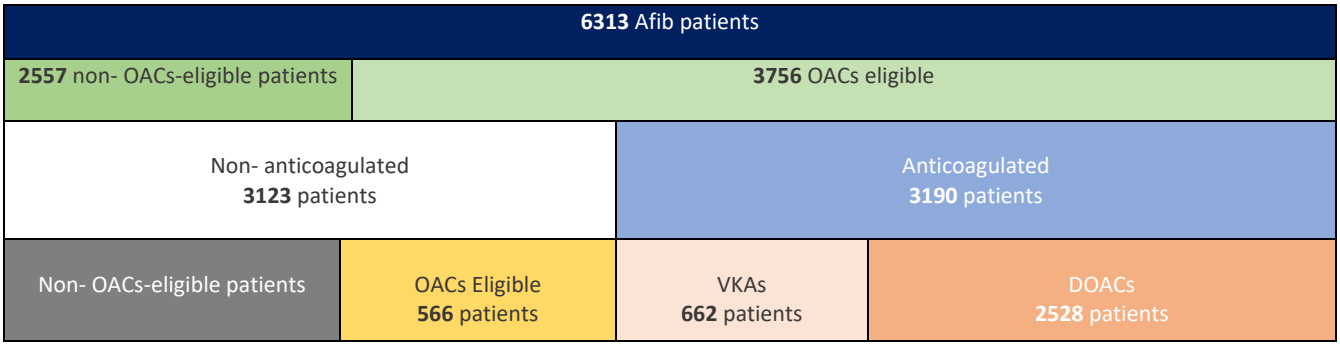
Figure 4. VKAs vs DOACs on a semester basis, from 2012-2019



Cost analysis

The total cost for all patients under VKAs in Flanders for 2019 was equal to 494 514 €/year. It included the total cost of VKA medications needed per patient per year, in addition to 15 yearly GP visits for INR monitoring. When a simulation of the total cost for these same patients was performed, considering they were under DOACs instead, we obtained an incremental cost of 498 486 €/DALY of prevented stroke. The incremental DALYs gained per prevented stroke is 770 based on the NNSw of 47 patients/ year multiplied by the burden of ischemic stroke of 55 DALY/person, thus yielding a corresponding incremental cost effectiveness ratio (ICER) of 647 €/DALY of prevented stroke (table 2; appendix 2).

Figure 5. Afib Flemish patients stratified by anticoagulation eligibility, 2019



For *scenario 2*, we considered the incremental cost of switching all anticoagulation eligible Afib Flemish patients in 2019 to DOACs, including the ones with a CHAD2DS2-VASc score of at least 2, while excluding the proportion who had a bleeding history. They make a total of 3,756 OACs-eligible patients, distributed between 662 already under VKAs, 2,528 already under DOACs and 566 patients who could potentially benefit from DOACs (graph 1). A corresponding ICER was 1,167 €/DALY of prevented stroke (table 2; appendix 2).

Table 2. Cost-utility analysis in Flanders, 2019

Scenario 1	**662** VKA → DOAC
Δ **cost (**€)	498,486 €
Prevented strokes	14
Δ **DALYs gained**	770
ICER (€/ DALY of prevented stroke)	**647**
Scenario 2	**3,756** OAC eligible → DOAC
Δ **cost (**€)	1,347,486 €
Prevented strokes	21
Δ **DALYs gained**	1,155
ICER (€/ DALY of prevented stroke)	**1,167**

Discussion

Main findings

The aim of our study was to analyze the pattern of OACs prescriptions in Flanders between 2002 and 2019 and to assess the benefit, in terms of DALYs, of switching patients from VKAs to DOACs. Through the longitudinal information provided by the INTEGO database, we were able to show that Afib cases increased overt time and within age groups in Flanders, with the highest proportions lying in the above 75 years old group. Specifically, the CHAD2DS2-VASc score ≥ 2 group had the highest proportion, especially for the last five years. Concurrently, an increase of Afib prevalence along the years is observed in patients older than 65 years old, reaching 13.5% in 2019 in the above 75 years old. The incidence follows the same trend increase and is also as high as 2.5% among the ≥ 75 years old group in 2019 also. These results are coherent with the aging population along the years, knowing that age is the most important risk factor for Afib in the general population. On the other hand, the loss to follow some patients in 2017 explains the decrease in prevalence because starting that year, INTEGO patients started being identified through their social security number instead of internal codes.

Our data shows a higher trend of OACs in the first year of Afib diagnosis in the CHAD2DS2-VASc scores of 1 and ≥ 2 since 2011, explained by the rise in DOACs use since their injection into the Belgian market, as VKAs proportions remain constant at around 10% along the years. Another reason is the lowered threshold of treatment with OACs due to the introduction of a more sensitive tool, the CHAD2DS2-VASc score, compared to the old CHADS2. The higher food and drug interactions of VKAs make DOACs the agents of choice when looking at top co-morbidities such as hypertension, bleeding history and renal dysfunction. Hypertension and renal dysfunction partially explain the predominance of use of beta-blockers and Ace inhibitors/AT2 antagonists.

Findings in perspective

The worldwide incidence rate and prevalence of Afib increased by 17% in 2017 compared to 2007 (W G. et al. 2019) The overall prevalence was 7.3% in 2016 in Italy and increased to as high as 16% with age, comparably to the numbers in Flanders (Di Carlo et al. 2019). According to the EurObservational Research Programme (EORP) registry, the proportion of ≥ 75 years old significantly increased over time, engendered by two reasons: first the higher screening of Afib patients, including asymptomatic ones, thus explaining the increased prevalence and incidence, and second the demographic transition accompanied by an enhanced management of cardiovascular diseases (Vitolo et al. 2020).

OAC prescription is strongly recommended in CHAD2DS2-VASc score ≥ 2 in men and ≥ 3 in women, while it should be considered for respective scores of 1 and 2 balancing the risk of bleed with the benefit of stroke reduction (Kirchhof P. et al.). On a national level, the GLORIA registry showed 80.1% use of anticoagulants in Belgium, ranking higher in comparison to other European countries (Cools et al. 2018).

In comparison with the UK between 2000 and 2016, the proportion of prescribed anticoagulants increased from 35.4% to 75.5% in CHAD2DS2-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 (Adderley et al. 2018). In Europe specifically, < 65-year-old patients are less prescribed OACs than ≥ 75 years old because of bleeding risk concerns (Koziel et al. 2021). Significant increase in OACs use was reported in the last 10 years: from 67% in EuroHeartSurvey (EHS) to 85% in EORP over the last decade in Europe (Vitolo et al. 2020). Factors associated with no OAC prescriptions in multimorbid Afib patients are the paroxysmal type of Afib, coronary artery disease, myocardial infarction and history of bleeding. As for factors associated with OAC use, they are: 65- 75 years old, a BMI ≥ 25 kg/m^2, 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 consequently strongly associated with greater frequency of OAC prescription (Koziel et al. 2021).

In the Belgian GLORIA registry, 14.5% were on VKAs and 65.6% on DOACs up to 2018, higher than our results in Flanders between 2015-2019 (Cools et al. 2018). In the GLORIA-AF registry, 83.8% were prescribed OACs among multi morbid cases, from which 60.2% were prescribed DOACs and 23.6% VKAs between 2014 and 2016. These numbers compare higher with our results, while prescription of antiplatelets was significantly lower (11% vs 26%), similarly in the EORP-AF registry (19.8% vs 26%) (Koziel et al. 2021 & Boriani et al. 2018). In the GARFIELD-AF registry, 51.4% DOACs and 48.6% VKAs were prescribed up to 2016, higher than our numbers, with less discrepancies between the two OAC types (Haas et al. 2019). Most common chronic comorbidities were hypertension, coronary disease and heart failure in the European Society of Cardiology (ESC-AF) registry (Lip et al. 2015). 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. The latter are preferred in declining renal function, age < 75 years old, myocardial infarction, congestive heart failure, diabetes mellitus and creatinine clearance < 60 mL/min (Koziel et al. 2021). In a 3-year follow-up from 2013 in the EORP-AF registry, a change from VKA to DOACs was observed in 5.4% of cases and was mainly associated with the concomitant diagnosis of coronary artery disease. As for the reverse switch, it was perceptible in 8.6% of cases and was associated with age and the presence of chronic heart failure (Boriani et al. 2018).

In Europe, stroke is the second most common cause of death and a leading cause of adult disability, associated with the demographic transition. Conversely, the declining trends in mortality and lost DALYs between 1990 and 2017 are expected to continue till 2047 (Wafa et al. 2020). A shift of stroke mortality to stroke morbidity is likely to be seen in the coming years due to two reasons: the 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 high sociodemographic index countries (Lippi et al. 2019). By itself, the ICER does not allow policy makers to draw conclusions about the efficiency of an intervention; a threshold value is required, beyond which the intervention is not considered profitable. The ICER cut-off could be defined as the society's willingness to pay (WTP) for a gained DALY based on the Welfarist economic theory (Cleemput et al. 2008). Because our results were calculated in a ratio of €/DALY, worth noting the difference between the two measurement tools of quality of life. The number of DALYs of a disease reflects the number of healthy life-years lost in a population due to the disease and considers four aspects of disease: the number of patients suffering from the disease, the severity of the disease, mortality and the age at death. In the cost-utility analyzes, 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 (Cleemput et al. 2008).

As decision making on the ICER threshold in Belgium remains an interactive deliberation process, a WTP threshold of 20 000 €/QALY was used as a reference. For both *scenarios*, they show to be cost-effective since they are below the threshold of 20 000 €/QALY. In comparison with a cost-effectiveness study on dabigatran, the latter showed 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 events hospitalization costs (Wouters et al. 2013).

Strengths

This study offers a comprehensive and updated overview of longitudinal information in Flanders since 2002 till 2019. It is a novel study specific to Flanders in combining an Afib descriptive epidemiologic part and the trend of OACs prescriptions along the years on one side, and a cost-utility analysis for all DOACs combined on the other. Additionally, it is the first study in Belgium accounting for a NNSw to show contemporary real cost-utility benefits of switching patients from VKAS to DOACs in 2019, while also offering simulation scenarios of switching patients from their current type of OAC to the other.

Limitations

Our study lost to follow some patients when INTEGO patients started being identified by their social security numbers starting 2017. Also, the numbers we have are restricted to the clinical practice setting, thus lacking hospitalized patients. Regarding the method to calculate the YLL, it 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 co-morbidities of the deceased, both interfering with the estimation of the YLL (Devleesschauwer et al.). On another side, the competing risk analysis is not taken into consideration; multimorbidity, highly present in the older population, has a high impact on mortality. Additionally, the NNSw retrieved from the systematic review is only an estimation not totally conformed to the Flemish population in terms of co-morbidities and age, limiting an exact extrapolation of the RR, while the study accounted for a two year follow up only. Also, the DOACs costs and the number of yearly GP visits for INR monitoring are only averages, bringing our results to estimations. Finally, the lack of ICER threshold bound our interpretations to assumptions, and the variability of healthcare systems around the world make it difficult to generalize our results to other countries.

Future implications

Switching to DOACs has shown to be beneficial and cost-effective. Still remains a huge potential at looking at patients from their multimorbidity perspective to better assess their prognosis. The demographic transition being a major cause for the European Union prevalence increase, we would be interested to explore how Afib prevalence, incidence increasing expectations and OACs prescription trends will be impacted by the parallel awareness rise in Afib screening and enhanced management. With respect to the

cost-effectiveness side, future roads worth exploring are the analysis change with different ICER thresholds, as well as with the introduction of DOACs generics into the market.

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Appendix 1

Relative Risk

- ≥ 75 years old

		Events		
		Stroke +	Stroke -	
Treatment (E+)	DOACs	388		13 576
	VKAs	449		11 133
				Total= 24 709

According to the article, the Relative Risk of stroke and systemic embolism (SE) for ≥ 75 years old is equal to 0.7 (26% risk reduction).

$RR = \left(\frac{388}{13576}\right) / \left(\frac{449}{11133}\right) = 0.709$

- $SE_{95\%}(ARR) = \sqrt{\frac{p1(1-p1)}{n1} + \frac{p2(1-p2)}{n2}} = 0.00235$
- $CI_{95\%}(ARR) = ARR \pm 1.96 * SE$
- $CI_{95\%}(NNSw) = 1 / (CI_{95\%}(ARR)) = [62.5 - 140]$

Absolute Risk Reduction

- ≥ 75 years old

$\left(\frac{449}{11133}\right) - \left(\frac{388}{13576}\right) = 0.0403 - 0.02858 = 0.01175$

Number Needed to Switch

- ≥ 75 years old
  1/ ARR= 1/ 0.01175= 85 patients

According to this article, we need to switch 85 patients who are ≥ 75 years old from VKAs to DOACs in order to prevent one stroke.

Appendix 2

The below calculation details the steps to obtain the cost of warfarin and DOACs, based on the BCFI and INAMI data

Generic name	Brand name	Afib dose	Tbs/box	Cost/month	Total price/year
Warfarin	Marevan©	6 mg/day	25 tablets	6 €	72 €
Apixaban	Eliquis©	10 mg/day	56 tbs*5 mg	78.23 €	940 €
Dabi 110	Pradaxa©	220 mg/day (reduced dose)	60 tbs* 110 mg	83.11 €	1000 €
Edoxaban	Lixiana ©	60 mg/day	28 tbs * 30 mg	78.2 € * 2	1 900 €
Rivaroxaban	Xarelto ©	20 mg/dose	30 tbs * 10 mg	86.75 € * 2	2 100 €

Cost of Warfarin

- Cost of INR= GP visit + INR cost= 45 €* 15= 675 € / person / year
- Cost of warfarin drug /year= 72 € / person/ year
- Total cost / year= 675 + 72 = 747 €/ person/ year

Cost of DOACs

- Average cost of DOAC/person/year= 1 500 €/ person/ year

Scenario 1: global benefit (cost of prevented stroke / DALY) of switching above 65-year-old patients in Flanders from VKAs to DOACs, based on the real 2019 number of patients under VKAs

- **Prevented strokes/ year**

- Patients > 65 years old in Flanders under VKAs in 2019: 662
- Number Needed to Switch: 85 cases in 1.8 years → 47 cases in 1 year
- 662/47= 14 prevented strokes/ year

- **Δ DALYs**

14 * 55= 770 DALYs gained

- **Δ cost**:

- Cost of VKA/ person= 747 €/person/year → Total cost= 747 * 662 patients= 494 514 €/ y
- Cost of DOAC/ person= 1500 €/person/year → Total cost= 1500 * 662= 993 000 €/ y
- Δ cost= 993 000- 494 514= 498 486 €

- **ICER**

ICER= 498 486 €/ 770 DALYs = 647 €/ DALY of prevented stroke

*Scenario 2***:** the global benefit (cost / DALY) if all eligible above 65-year-old patients in Flanders with Afib were put under DOACs in 2019

- **Prevented strokes/ year**

- Patients > 65 years old with Afib in Flanders in 2019: 6313
- 85% eligible * 70% (CHAD2DS2-VASc= 2) = 3756
- Number Needed to Switch: 47 cases in 1 year

- Number Needed to Treat: 83 cases
- 662 VKA / NNSw= 14
- 566 OACs free eligible/ NNT= 566/ 83 = 7
- Total = 14 +7= 21 prevented strokes /year

▪ **Δ DALYs**

21* 55= 1155 DALYS gained

▪ **Δ cost**

- Total cost (patients under OACs) = 1500 * 2528 + 747* 662 = 4 286 514 €/ y
- Total cost (patients put under DOACs) = 1500 * 3756= 5 634 000 €/ y
- Δ cost= 5 634 000 - 4 286 514 = 1 347 486 €

▪ **ICER**

ICER= 1 347 486 / 1155= 1167 €/ DALY of prevented stroke