Evolution and trends of atrial fibrillation, anticoagulation therapy and its effect on cerebrovascular events in primary care: a registry-based study in Flanders

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Master of Family Medicine

Masterproef Huisartsgeneeskunde
Academiejaar: 2022– 2023

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ABSTRACT

Context: Voorkamerfibrillatie (VKF) is de meest voorkomende hartritmestoornis. Patiënten met VKF hebben meer comorbiditeiten en een verhoogd risico op een cerebrovasculair accident (CVA). Heden kunnen zowel vitamine K antagonisten als directe orale anticoagulantia gebruikt worden in de preventie van ischemische beroertes na VKF.

Doel: Het doel van deze studie is een update geven in de evolutie van de incidentie en prevalentie van VKF, het gebruik van orale anticoagulantia na VKF en de associatie van comorbiditeiten met het ontstaan van VKF en een CVA in de voorbije 20 jaar.

Methoden: We verzamelden data uit de Intego databank, met gegevens van een Vlaams huisartsenregistratienetwerk van 2002 tot 2022. We includeerde patiënten die ouder waren dan 18 jaar en minstens één contact hadden met hun huisarts. Hieruit werden patiënten met een nieuwe diagnose van VKF én minstens een jaar aan opvolging geselecteerd voor een subanalyse en werden deze gematcht aan 3 of 4 controlepatiënten.

Resultaten: We detecteerden 9620 patiënten met een nieuwe diagnose van VKF. Patiënten met VKF hadden een hogere CHA_2DS_2 VASc score (2.8±1.6 vs 2.5±1.5; $p<0.05$) en mCCI (0.9±1.3 vs 0.7±1.2) dan controlepatiënten. Er was een significante stijging van de incidentie en prevalentie de voorbije 20 jaren met in 2017-2022 een incidentie van 3.7/1000 patiëntjaren (PY) en prevalentie 7.7%. De incidentie en prevalentie van VKF steeg met de leeftijd. De CHA_2DS_2-VASc score (odds ratio (OR) 1.09; 95% betrouwbaarheidsinterval (CI) 1.05-1.12) en mannelijk geslacht (OR 1.07; 95% CI 1.01-1.13) waren onafhankelijk geassoceerd met detectie van VKF. Er was een significante stijging in het gebruik van orale anticoagulantia na VKF (average annual percent change (AAPC) 3.4%; $p<0.05$) en meer specifiek in de groep met een CHA_2DS_2 VASc score ≥2 (AAPC 4.7%; $p<0.05$). Er was een significant dalende trend in de categorie met laag risico op een CVA na VKF (AAPC -2.0; $p<0.05$). Na multivariate analyse was enkel diabetes mellitus geassocieerd met een verhoogd risico op een beroerte na VKF (hazard ratio (HR) 1.86; 95% CI 1.37-2.36). Meer dan 20% van de patiënten met VKF en een CHA_2DS_2-VASc score ≥ 2 werd gediagnosticeerd met een CVA.

Conclusie: De incidentie en prevalentie van VKF steeg significant de voorbije 20 jaren en groeide met de leeftijd. We toonden verschillende behandelbare comorbiditeiten geassocieerd met het ontwikkelen van VKF en een beroerte. Er was reeds een verbetering in de anticoagulerende aanpak van VKF, maar verdere toename in behandeling volgens de huidige richtlijnen is nodig.

ABSTRACT

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia with patients having significantly more comorbidities and an increased risk of stroke. At present both vitamin K antagonists and direct oral anticoagulants can be used in the prevention of a cerebrovascular event.

Aim: In this registry-based study, we aimed to give an update on the evolution of AF incidence and prevalence, the use of oral anticoagulants and the association of comorbidities with both onset of AF and a cerebrovascular event over the past two decades.

Methods: Data were obtained from the Intego database, a Flemish general practice-based registration network with data from 2002 up to 2022. Patients ≥ 18 years old and at least one contact with their general practitioner were included. Patients with a new diagnosis of AF and follow-up of at least one year were included in the subanalysis of this study and were matched to 3 or 4 control patients.

Results: We detected 9620 cases of new-onset AF. These patients had a higher CHA_2DS_2 VASc score (2.8±1.6 vs 2.5±1.5; $p<0.05$) and mCCI (0.9±1.3 vs 0.7±1.2) compared to controls. We observed a significant increase in incidence and prevalence of AF with incidence 3.7/1000 person years (PY) and prevalence 7.7% in 2017-2022. Both incidence and prevalence rates increased with age. The CHA_2DS_2-VASc score (odds ratio (OR) 1.09; 95% confidence interval (CI) 1.05-1.12) and male gender (OR 1.07; 95% CI 1.01-1.13) were independently associated with AF detection. A significant increase in the use of oral anticoagulants was observed with average annual percent change (AAPC) 3.4% ($p<0.05$) over the period 2002-2022, especially in the category with CHA_2DS_2 VASc score ≥2 (AAPC 4.7%; $p<0.05$). A significant decreasing trend was observed in the category with a low risk for stroke (AAPC -2.0%; $p<0.05$). In a multivariate analysis, only diabetes mellitus was associated with an increased risk of stroke, hazard ratio (HR) 1.86 (95% CI 1.37-2.36). More than one fifth of the patients with detected AF and a CHA_2DS_2-VASc score ≥2 developed stroke in this study.

Conclusion: The incidence and prevalence of AF significantly increased over the past two decades and increased with age. Treatable comorbidities were shown to be associated with the development of AF and stroke. We observed an improvement in correct anticoagulation therapy after AF, but further increase in treatment according to the guidelines is needed to reduce the risk of stroke.

USED ABBREVIATIONS

Atrial fibrillation (AF)

European Society of cardiology (ESC)

Oral anticoagulants (OAC)

Vitamin K antagonists (VKA)

Direct oral anticoagulant (DOAC)

General practice/General practitioner (GP)

International classification of primary care - 2 (ICPC-2)

International statistical classification of diseases and related health problems, 10th revision (ICD-10)

World Health Organization (WHO)

Anatomical Therapeutic Chemical (ATC)

Modified Charlson comorbidity index (mCCI)

Charlson comorbidity index (CCI)

Average annual percent change (AAPC)

Transient ischemic attack (TIA)

Cerebrovascular accident (CVA)

Person years (PY)

Odds ratio (OR)

Hazard ratio (HR)

BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia with increasing incidence and prevalence due to improving detecting methods of AF, increasing life expectancy and multimorbidity (1). The prevalence of AF in the European Union is expected to double from 2010 to 2060 with an estimated prevalence of 17.9 million adults with AF in 2060 (2). Patients with AF have significantly more comorbidities and AF is known to increase the risk of thrombo-embolic events (3,4). Besides rhythm control, rate control and managing cardiac risk factors and comorbidities, the prevention of stroke and systemic thromboembolisms is an important part of the AF management.

Current 2020 guidelines from the European Society of Cardiology (ESC) use the CHA_2DS_2-VASc score to estimate the risk of stroke in patients with AF, with a correction for gender (5). Patients at high risk for stroke (CHA_2DS_2-VASc score ≥ 2 in males or ≥ 3 in females) should be treated with an (oral) anticoagulant (OAC), whereas patients with a low risk for stroke (CHA_2DS_2-VASc score = 0 in males or 1 in females) would not benefit from the anticoagulation therapy. In the grey zone between high- and low-risk patients, anticoagulation therapy should be individually considered, taking into account the bleeding risk. However, patients with a high risk for thromboembolisms were undertreated in a Belgian cohort from a prospective observational study, as 15.8% did not receive anticoagulation therapy (6). Low-risk patients were frequently overtreated, with 58.7% of these patients treated with an OAC.

Until 2009, Vitamin K antagonists (VKA) were the only available oral anticoagulants. These OAC reduced the risk of ischemic stroke by two-thirds compared to placebo, but are known to have a narrow therapeutic window, the need for frequent monitoring and are prone to drug-drug and nutritional interactions (7). In the past decade, the use of direct oral anticoagulants (DOACs or NOACs) is on the rise. These drugs are shown to be as effective as VKA in the prevention of stroke and systemic embolisms with a significant reduced risk of hemorrhagic bleeding, no need for therapeutic monitoring and rapid on- and offset, but an increased gastrointestinal bleeding risk (8–10). The current ESC guidelines (2020) prefer the use of DOACs over VKA for the prevention of thromboembolisms after AF (5).

At present there is no study that investigated the use of all four direct oral anticoagulants (apixaban, dabigatran, rivaroxaban and edoxaban) in general practices in Belgium. Furthermore, there are few international studies describing the long-term use of direct oral anticoagulants in a primary care setting since their introduction. With rapidly evolving detecting methods, increasing electronic registration of consults and diagnoses by physicians and (semi) mandatory electronic prescribing of drugs, plenty valuable data is available.

In this registry-based study, we aimed to give an update on the evolution of incidence and prevalence of AF over the past two decades in a primary care setting (General Practice) in Flanders (Belgium) and the association between comorbidities and onset of AF. Additionally, we studied the use of oral anticoagulants in patients with detected AF and comorbidities associated with a higher risk of a cerebrovascular event after AF. We compared the incidence and prevalence of AF to international data and studied whether the trend in prescribing oral anticoagulants after AF is in line with the current guidelines.

METHODS

Study design

In this registry-based study, data was extracted from the Intego database. Intego is a general practice (GP) based registration network that extracts data from medical electronic health records (Medidoc® and Care Connect®, Corilus NV, Ghent, Belgium) in over 100 practices in Flanders (Belgium) (11). The Intego database is a project of the Department of Public Health and Primary Care of the KU Leuven. The patient population in the Intego database is a representation of the population in Flanders, regarding age, sex and social class or income. We used the yearly contact group as the denominator (population at risk) in this study, defined as the number of unique patients that visited their GP at least once in a given year. (11,12) Patient background, new diagnoses, drug prescriptions and laboratory results are routinely extracted from the selected practices, are encrypted, and collected in the Intego central database. Diagnoses were registered in the Intego database according to the International Classification of Primary Care (ICPC-2) or International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) and drug prescriptions according to the WHO's Anatomical Therapeutic Chemical (ATC) classification. This study extracted new diagnosis of atrial fibrillation and age of diagnosis, a history of atrial fibrillation, the use of oral anticoagulants and antiplatelet therapy after diagnosing AF and the CHA_2DS_2-VASc score (history of congestive heart failure, arterial hypertension, age 75 years or older, diabetes mellitus, prior thrombo-embolism or stroke, vascular disease, age 65 to 75 years and female gender). Furthermore, we checked for a registration of other comorbidities needed to calculate the modified Charlson Comorbidity Index (mCCI; myocardial infarction, dementia, chronic pulmonary disease, peptic ulcer, liver disease, hemiplegia, moderate to severe renal disease, cancer, leukemia, and lymphoma).

Study population

The Intego database was searched for all patients who were 18 years and older and had at least 1 contact with their GP since January 1st, 2002. Of these patients, the ones with a new diagnosis of AF

and a follow-up of 1 year and longer after the diagnosis of AF were included in the subanalysis of this study. For each patient with a new diagnosis of AF 3 or 4 control patients were matched (13). These patients were matched for age, gender, and GP but without diagnosis of AF.

Outcome variables

The primary outcome in this study was a diagnosis of AF, International Classification of Primary Care (ICPC-2)-code K78. Comorbidities were checked and compared between cases and controls. These comorbidities were checked for all cases and controls individually using the CHA_2DS_2-VASc score and modified Charlson Comorbidity Index (mCCI) (4,14).

The CHA_2DS_2-VASc score was calculated using the patient background data for a history of congestive heart failure (ICPC-2 code K77; 1 point), arterial hypertension (ICPC-2 code K86 or K87; 1 point), age ≥75 years (2 points), diabetes mellitus (ICPC-2 code T89 or T90; 1 point), prior stroke or thrombo-embolism (ICPC-2 code K89 or K90; 2 points), a history of vascular disease (prior myocardial infarction, peripheral arterial disease or aortic plaque; ICPC-2 code K75 or K93; 1 point), age 65-74 years (1 point) and the female gender (1 point) (5,15).

The Charlson Comorbidity Index (CCI) includes 19 chronic diseases, weighted for their association with mortality. In this study we used a modified version of the CCI. (4) We checked the patient history for the registration of diabetes mellitus (ICD10 E10-14; 1 point), myocardial infarction (ICD10 I21, I22, I25.2; 1 point), cerebrovascular event (ICD10 G45, G46, H34.0, I60–I69; 1 point), peripheral arterial illness (ICD10 I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9; 1 point), chronic pulmonary disease (ICD10 I27.8, I27.9,J40–J47, J60–J67 J68.4, J70.1, J70.3; 1 point), moderate to severe renal disease (ICD10 I12.0, I13.1, N03.2–N03.7, N052–N05.7, N18, N19, N25.0, Z49.0–Z49.2, Z94.0, Z99.2; 2 points), peptic ulcer (ICD10 K25-28; 1 point), dementia (ICD10 F00–F03, F05.1, G30, G31.1; 1 point), liver disease (ICD10 B18, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73, K74, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4; 1 point), hemiplegia (ICD10 G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9; 2 points), cancer (ICD10 C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97; 2 points), leukemia (ICD10 C91-C95; 2 points), lymphoma (ICD10 C81-C86; 2 points) and AIDS/HIV (ICD10 B20–B22, B24; 6 points) (16).

Secondary outcome variable was the start of oral anticoagulation therapy after the diagnosis of AF. Anticoagulants were divided into VKA warfarin, phenprocoumon, acenocoumarol (ATC code respectively B01AA03, B01AA04, BO1AA07) and DOAC's rivaroxaban, apixaban, edoxaban, dabigatran (ATC code respectively B01AF01, B01AF02, B01AF03, B01AE07). If different anticoagulants were prescribed for one patient, the last prescribed anticoagulant was included.

Tertiary outcome was a diagnosis of cerebrovascular event after the diagnosis of AF. We searched the patient history for cerebrovascular accident (CVA) and transient ischemic attack (TIA). The risk of cerebrovascular events was calculated.

Data analysis

The prevalence and incidence of AF were calculated for each yearly contact group. Continues data were described as a mean with standard deviation (SD). Categorical data were described as numbers and frequencies. An independent samples two-sided t-test was used for the comparison of continues data and a X^2 test was used to compare categorical data between cases and controls. The package of Pavlos Mamouris was used for the case-control study.

The association between comorbidities and AF was explored using a bivariate and multivariate regression analysis and expressed in odds ratio with a 95% confidence interval. Comorbidities were explored individually and by using the CHA_2DS_2-VASc score and modified Charlson Comorbidity Index.

Trends in incidence and prevalence of AF and in prescriptions of OAC after diagnosis of AF were analyzed using a joint point regression analysis. (17) A joinpoint is defined as a point on the trend curve with a statistically significant change in trend. An annual percent change (APC) and average annual percent change (AAPC) were extracted from the joinpoint analysis to describe the trends in the prescriptions of OAC yearly and averaged over a period of 2 decades. The SEER*Stat software (Joinpoint Trend Analysis software from the Surveillance Research Programme of the US National Cancer Institute (http://surveillance.cancer.gov/jointpoint)) was used for the trend analysis. (18–20)

The risk of a cerebrovascular events (TIA or CVA) after diagnosis of AF was calculated using a Cox proportional hazards model and adjusted for age and gender. We used a Kaplan-Meier time-to-event analysis to analyze the time to cerebrovascular event after AF.

Data processing and statistical analysis were performed by L-Biostat (Leuven, Belgium) using software program R version 4.2.3 for these analyses. Statistical significance was set at $p<0.05$.

Ethics Approval

This study is part of the Intego project. The procedures of the Intego project were approved by the ethical review board of the Faculty of Medicine of the KU Leuven (number ML1723) and by the Belgian privacy commission (number SCSZG/13/079).

RESULTS

Epidemiology

A total of 660,476 unique patients were ≥18 years old and had at least one contact with their GP between 2002 and 2022. There were 9620 cases of new onset AF registered with a follow-up of at least 1 year. Patients with a new diagnosis of AF had a mean age of 74.2 years, with more than half of them male (53.2%). Compared to the control group matched for age, gender and GP, patients with AF had significantly more comorbidities, with a higher CHA_2DS_2 VASc score (2.802 ± 1.607 vs. 2.485 ± 1.534; p<0.05) and a higher mCCI (0.946 ± 1.288 vs. 0.694 ± 1.155; p<0.05). All individual risk factors of the CHA_2DS_2 VASc score were significantly more present in the AF group. There was no significant difference in history of leukemia (Table 1).

The overall age- and sex standardized incidence was 3.7/1000 person years (PY) between 2017 and 2022 versus 2.4/1000PY between 2002 and 2006 (p<0.05). Incidence rates increased significantly over the past 20 years in men as well in women. Incidence rates increased with age (Figure 1), with 23.9/1000PY in the category ≥85 years versus 0.8/1000PY in the category 18-64 years between 2017 and 2022 (Table 2).

Prevalence of AF significantly increased with a prevalence of 7.7% in 2017-2022 versus 5.3% in 2002-2006. The prevalence of AF was higher in older age categories with 15.3% in patients ≥85 years versus 0.5% in patients 18-64 years between 2017 and 2022 (Table 3).

Comorbidities and development of atrial fibrillation

A univariate analysis showed an increasing CHA_2DS_2 VASc score (odds ratio (OR) 1.28; 95% confidence interval (CI) 1.25-1.30, p<0.05) and mCCI (OR 1.18; 95% CI 1.16-1.20, p<0.05) were associated with development of AF. Dementia was associated with a lower risk of AF diagnosis, with OR 0.85 (95% CI 0.694-0.996, p<0.05). After multivariate analysis an increasing age (OR 1.01; 95% CI 1.006-1.012, p<0.05), male gender (OR 1.07; 95% CI 1.01-1.13, p<0.05) and increasing CHA_2DS_2 VASc score (OR 1.09; 95% CI 1.05-1.12, p<0.05) were associated with a higher risk of AF. Dementia remained associated with a lower risk of AF detection after multivariate analysis (OR 0.74; 95% CI 0.58-0.89, p<0.05) (Table 4-5).

Anticoagulation therapy

The use of oral anticoagulants was significantly higher after a diagnosis of AF. In 2022 46.8% of the patients with registered AF was treated with an oral anticoagulant, 42.1% on a DOAC and 4.7% on a VKA. All oral anticoagulants, except for edoxaban were significantly more prescribed in cases than in

controls with 66.0% receiving a DOAC and 30.9% a VKA after AF. Apixaban and rivaroxaban remained the most prescribed DOAC, respectively 30.5% and 24.6% (Table 6).

Between 2002 and 2022 there was a gradual increase in the use of oral anticoagulants in the high-risk category (CHA_2DS_2 VASc score ≥2) with an AAPC of 4.7% ($p<0.05$) and a decrease in the low-risk category (CHA_2DS_2 VASc score = 0) with an AAPC of -2.0% ($p<0.05$). No significant increasing or decreasing trend was observed in the intermediate-risk category over the past two decades (Table 7). Regardless of the CHA_2DS_2 VASc score, there was an overall increase in prescriptions of oral anticoagulants after AF (3.4%; $p<0.05$). In the low-risk category there was no significant trend in OAC prescriptions between 2002 and 2007, however from 2007 up to 2022 a significant decreasing trend in OAC prescriptions after AF was observed (APC 2007-2022 -3.4%; $p<0.05$). In the high-risk category there was a significant increasing trend between 2002 and 2015 with APC 6.7% ($p<0.05$) with no significant upward or downward trend after 2015. In all risk groups there was a clear increase in the number of prescribed DOACs at the expense of VKA with DOACs getting the upper hand in 2014 (CHA_2DS_2 VASc score ≥ 2), 2015 (CHA_2DS_2 VASc score = 1) and 2018 (CHA_2DS_2 VASc score = 0) (Figure 2).

Cerebrovascular event

After a mean follow-up time of 205 months more than one fifth of the patients with AF had developed a CVA in the category with a CHA_2DS_2 VASc score ≥ 2 (Figure 3). In a univariate analysis increasing CHA_2DS_2 VASc score (HR 1.38, 95% CI 1.22-1.54; $p<0.05$) and hypertension (HR 1.50, 95% CI 1.12-1.89; $p<0.05$) were associated with a higher risk of a cerebrovascular event (Table 8). Diabetes mellitus was the strongest predictor of a cerebrovascular event after diagnosis of AF with HR 1.86 (95% CI 1.38-2.33; $p<0.05$). After multivariate analysis, only diabetes mellitus showed to be associated with a significantly increased risk of a cerebrovascular event after AF (HR 1.86, 95% CI 1.37-2.36; $p<0.05$) (Table 9).

DISCUSSION

This study showed a significantly increasing incidence and prevalence of AF over the past two decades, with higher incidence and prevalence rates in older age categories. A burden of comorbidities in this study have shown to be independently associated with the development of AF. After a diagnosis of AF, we detected a significant positive trend in prescriptions of oral anticoagulants in the group with a high risk for stroke and a significant downward trend in prescribing oral

anticoagulants to patients with a low risk of stroke. Hereby, the discrepancy between current guidelines and treatment patterns reduced over the past two decades.

Epidemiology of atrial fibrillation

Patients with a diagnosis of AF in this study had a mean age of 74.2 years and had a mean CHA_2DS_2 VASc score of 2.8. These data were comparable with studies in the UK, Iceland, New Zealand and Germany (21–25). Of the patients with newly-onset diagnosis of AF, more than half (53%) was male. Incidence and prevalence rates were higher in males than in females, regardless of age. AF therefore remains a male dominant diagnosis, as already described in the Rotterdam study (26).

The overall age- and sex standardized incidence rate in our study was 2.4/1000PY in 2002-2006 and 3,7/1000PY in 2017-2022. These results are in line with a large German study, observing an overall incidence of 4.4/1000PY in men and 3.9/1000PY in women in 2007-2008 (22). This German study had a similar study population with a mean CHA_2DS_2 VASc score 2.8 and mean age 73.1 years. Incidence rates were higher in a study by Vanbeselaere et al. (6.4/1000PY in 2002 and 8.3/1000PY in 2011) and in the Rotterdam study (9.9/1000PY between 1990 and 2000) (4,26). This may be due to differences in inclusion criteria, as these two latter studies only included patients with an age of ≥55 years and ≥60 years, respectively. We observed an increase in incidence rates with age. As we compared our data to the existing literature, this trend was also described in the UK, Germany and the Netherlands (22,24,26). We detected a significant increase in incidence and prevalence rates of AF between 2002 and 2022 with 5.3% in 2002-2006 and 7.7% in 2017-2022. Vanbeselaere et al. showed a comparable increase in prevalence with 5.3% in 2002 and 6.4% in 2011, with an older study population (4). Prevalence in a UK study between 2000 and 2016 increased from 2.02% in 2000 to 3.29% in 2016 (21).

Comorbidities and development of atrial fibrillation

In addition to the CHA_2DS_2 VASc score, increasing age, congestive heart failure, hypertension, a cerebrovascular event, peripheral vascular disease, chronic pulmonary disease, liver disease or history of cancer have shown to be independently associated with a diagnosis of atrial fibrillation. These results are similar to the findings of Vanbeselaere et al. between 2002 and 2011 in an older study population (4). Patients with a history of dementia were associated with a lower risk of AF diagnosis in our study. This may be due to higher mortality rates, difficulties with expression, hidden symptoms, or asymptomatic presentation of these patients.

Anticoagulation therapy

Overall, there was an increase in the use of oral anticoagulants after AF between 2002 and 2022, with an AAPC of 3.4%. However, we detected a significant increasing trend in the category at high risk for stroke with AAPC of 4.7% with only an increasing trend between 2002 and 2015, no significant increasing trend was observed after 2015. In the low-risk category a significantly decreasing trend was observed since 2007. With decreasing underuse and overuse over the past two decades, the discrepancy between treatment patterns and current guidelines of AF treatment was reduced. We observed a significant increase in the use of DOACs at the expense of VKA in all risk categories. DOACs already dominated the high-risk category in 2014, and only in 2015 and 2018 in the intermediate- and low-risk categories. Of the DOACs, apixaban and rivaroxaban remained the most prescribed, the prescription of dabigatran stagnated and edoxaban was prescribed very rarely for patients with new-onset AF in this study. Edoxaban was only reimbursed in Belgium in 2016, the use of newer DOACs may therefore not be sufficiently known, and GPs tend to adhere to prescribing habits as there is no DOAC proven to be significantly more effective (27).

Our data matched the results of a large international prospective study on the use of oral anticoagulants after AF (GARFIELD), with increasing use of oral anticoagulants and more specific DOACs in the last decade in patients with a high-risk of stroke (28). In the high-risk category of the GARFIELD study, 69% of the patients received an oral anticoagulant, with major geographic variability from 31% to 93% treated with an oral anticoagulant. The GARFIELD study showed DOACs were prescribed in 3% of the patients with AF in 2010 whereas 43% was prescribed a DOAC in 2016. Similar patterns were shown in the ORBIT-AF I and ORBIT-AF II study in the United States (29,30). Data from the Belgian cohort of the GARFIELD study showed an overall increase of prescriptions of oral anticoagulants in patients with AF from 73.1% in 2012 up to 84.7% in 2016 (6). These figures are higher than the proportion of patients with AF covered with an oral anticoagulant in our study. The mean age of patients in the Belgian cohort of the GARFIELD study was 71.3 years, whereas with a score of 3.1, the mean CHA_2DS_2 VASc score was higher than in our study. This may be because the GARFIELD study mainly gathered data from hospital records and only a few from primary care records. Our data was obtained only from primary care records. In a German study, a history of dementia and the prescribing pattern of individual general practitioners were described as the main cause for underuse of oral anticoagulants in patients with AF and a high risk for stroke (31).

Cerebrovascular event

More than one fifth of the patients with a new diagnosis of AF and a CHA_2DS_2 VASc score ≥ 2 suffered a cerebrovascular event between 2002 and 2022. We showed in a univariate analysis an increasing

CHA_2DS_2 VASc score (HR 1.38) and hypertension (HR 1.50) to be associated with a higher risk of a cerebrovascular event. However, only diabetes mellitus (HR 1.86) was shown to be an independent predictor of a cerebrovascular event in this study. An earlier study using the Intego database with data registered between 2002 and 2011 showed increasing age (HR 1.05), CHA_2DS_2 VASc score (HR 1.4) and renal disease (HR 1.3) to be associated with a higher risk of a cerebrovascular event after AF (4). Renal disease was not included in our data, because of a complete separation problem.

This study has shown that knowledge of current guidelines on AF management and treatment in accordance with these guidelines improved over the past 20 years, but room for further improvement remained. As in comparable studies, we have shown treatable comorbidities to increase the risk of AF and a cerebrovascular event after AF. This suggests a vigilance is required from primary health care workers in the detection and management of these comorbidities to reduce the risk of AF and cerebrovascular events.

Strengths and limitations of this study

Our study described two decades of data registered in a large Flemish database of primary care records and was therefore representative for the general population in Flanders, Belgium. In 2022 we had data of over 10 years of DOAC usage in Belgium. Main limitations of this study were due to database limitations. There was no data on loss to follow-up, with no mortality data. We had no data on individual bleeding risk (e.g., HASBLED score). As this was a registry-based study, we depended on the quality of registration and coding of medical records by general practitioners. There was no registration of manually prescribed anticoagulants, as often used by general practitioners on home visits or in nursing home facilities. We had no data from hospital records or follow-up of patients by a cardiologist in private practices. The use of electronic prescribing methods in nursing home facilities is increasing recently, therefore updated studies combining data from primary care records, hospital records and nursery facility records are needed for an accurate representation of the general population.

CONCLUSION

Atrial fibrillation is the most common cardiac arrhythmia with increasing incidence and prevalence. These patients are high at risk for stroke, with more than one fifth of the patients diagnosed with a cerebrovascular event after AF in the past two decades. This study showed a range of comorbidities to be vigilant in the prevention of atrial fibrillation and stroke. We showed a significant increasing trend of correct anticoagulation of patients with atrial fibrillation and a high risk for stroke. Direct

oral anticoagulants took over the market of anticoagulants in the last 10 years at the expense of vitamin K antagonists and are considering their safety and efficacy profile jointly responsible for this trend in anticoagulation therapy. Further studies are needed combining data of primary care, hospital, and nursing home facility records for the most accurate representation of atrial fibrillation incidence, oral anticoagulation therapy and development of cerebrovascular events.

Tables and Figures

Table 1. Patient characteristics and demographics

	Atrial fibrillation n= 9620	**Control n= 28078**	**P-value**
Age (years), mean ± SD	74.228 ± 12.250	73.969 ± 12.229	0.074
Sex (men), n (%)	5115 (53.170)	14940 (53.209)	0.474
CHA_2DS_2-VASc score, (mean ± SD)	2.802 ± 1.607	2.485 ± 1.534	0*
Modified Charlson Comorbidity Index (mCCI), (mean ± SD)	0.946 ± 1.288	0.694 ± 1.155	0*
Myocardial infarction, n (%)	5.000 (0.052)	13.000 (0.046)	0.413
Congestive heart failure, n (%)	683.000 (7.100)	998.000 (3.554)	0*
Hypertension, n (%)	4009.000 (41.674)	8569.000 (30.519)	0*
Diabetes Mellitus, n (%)	1339.000 (13.919)	2904.000 (10.343)	0*
Cerebrovascular event, n (%)	864.000 (8.981)	1522.000 (5.421)	0*
Peripheral vascular disease, n (%)	447.000 (4.647)	843.000 (3.002)	0*
Dementia, n (%)	230.000 (2.391)	776.000 (2.764)	0.025*
Chronic pulmonary disease, n (%)	1890.000 (19.647)	3835.000 (13.658)	0*
Peptic ulcer, n (%)	231.000 (2.401)	516.000 (1.838)	0*
Liver disease, n (%)	339.000 (3.524)	665.000 (2.368)	0 *
Renal disease, n (%)	814.000 (8.462)	1718.000 (6.119)	0*
Cancer history, n (%)	915.000 (9.511)	2158.000 (7.686)	0*
Leukemia, n (%)	47.000 (0.489)	106.000 (0.378)	0.070

*Indicates p-value<0.05

Table 2. Trends in incidence of atrial fibrillation by age and sex

	Incidence (/1000PY)				
	2002-2006	2007-2011	2012-2016	2017-2022	p-value
Male					
All ages	2,7	3,0	3,7	4,3	0*
<65 years	1,0	1,1	1,3	1,3	0,001*
65-74 years	7,6	8,0	9,9	9,4	0,002*
75-84 years	12,9	13,1	15,5	18,9	0*
>85 years	10,6	16,0	19,4	26,3	0*
Female					
All ages	2,1	2,3	2,8	3,2	0*
<65 years	0,4	0,4	0,6	0,5	0,479
65-74 years	4,6	5,7	5,8	5,5	0,186
75-84 years	10,5	9,7	12,5	13,7	0*
>85 years	10,7	12,8	16,7	22,7	0*
Male & female					
All ages	2,4	2,6	3,2	3,7	0*
<65 years	0,7	0,7	0,9	0,8	0,003*
65-74 years	6,0	6,8	7,7	7,3	0,001*
75-84 years	11,5	11,1	13,8	15,9	0*
>85 years	10,7	13,8	17,6	23,9	0*

*Indicates p-value<0.05

Table 3. Trends in prevalence of atrial fibrillation by age and sex

	Prevalence (%)				
	2002-2006	2007-2011	2012-2016	2017-2022	p-value
Male					
All ages	6,4	7,5	8,5	9,6	0*
<65 years	0,6	0,6	0,7	0,8	0*
65-74 years	4,6	5,6	6,6	6,4	0*
75-84 years	9,1	9,9	11,6	13,0	0*
>85 years	11,3	13,9	15,1	18,2	0*
Female					
All ages	4,6	5,2	6,0	6,4	0*
<65 years	0,2	0,2	0,3	0,3	0,001*
65-74 years	2,7	2,9	3,6	3,1	0*
75-84 years	6,1	7,2	8,0	8,4	0*
>85 years	9,2	10,4	12,1	13,9	0*
Male & female					
All ages	5,3	6,1	7,1	7,7	0*
<65 years	0,4	0,4	0,5	0,5	0*
65-74 years	3,6	4,2	5,1	4,7	0*
75-84 years	7,3	8,3	9,5	10,4	0*
>85 years	9,9	11,5	13,1	15,3	0*

*Indicates p-value<0.05

Table 4. Univariate analysis of the association between comorbidities and the development of atrial fibrillation

	Bivariate OR	95% CI low	95% CI high	P-value
Age (per year increase)	1.00	0.9998	1.0036	0.073
Age group,				
65-74 years	1.01	0.94	1.08	0.833
75-84 years	1.02	0.96	1.09	0.534
>85 years	1.07	0.997	1.143	0.068
Sex (men)	1.00	0.95	1.04	0.948
CHA_2DS_2-VASc score (per point increase)	1.28	1.25	1.30	0*
Comorbidity				
Charlson Comorbidity Index (per point increase)	1.18	1.16	1.20	0*
Myocardial infarction	1.11	0.08	2.15	0.837
Congestive heart failure	2.08	1.98	2.18	0*
Hypertension	1.64	1.59	1.69	0*
Diabetes Mellitus	1.40	1.33	1.47	0*
Cerebrovascular event	1.72	1.63	1.81	0*
Peripheral vascular disease	1.57	1.45	1.68	0*
Dementia	0.85	0.694	0.996	0.028*
Chronic pulmonary disease	1.54	1.48	1.60	0*
Peptic ulcer	1.31	1.15	1.47	0.001*
Liver disease	1.51	1.38	1.64	0*
Hemiplegia	1.48	1.10	1.86	0.045*
Renal disease	1.41	1.33	1.50	0*
Cancer history	1.26	1.18	1.34	0*
Leukemia	1.29	0.94	1.63	0.15
Lymphoma	1.22	0.90	1.54	0.216
AIDS/HIV	0.85	-0.73	2.42	0.834

*Indicates p-value<0.05

Table 5. Multivariate analysis of the association between comorbidities and the development of atrial fibrillation

	Multivariate OR	95% CI low	95% CI high	P-value
Age (per year increase)	1.01	1.006	1.012	0*
Sex (men)	1.07	1.01	1.13	0.0295*
CHA_2DS_2-VASc score (per point increase)	1.09	1.05	1.12	0*
Comorbidity				
Myocardial infarction	0.97	-0.07	2.01	0.9531
Congestive heart failure	1.59	1.48	1.70	0*
Hypertension	1.36	1.29	1.42	0*
Diabetes Mellitus	1.05	0.97	1.13	0.2547
Cerebrovascular event	1.30	1.19	1.41	0*
Peripheral vascular disease	1.19	1.07	1.32	0.0045*
Dementia	0.74	0.58	0.89	0.0001*
Chronic pulmonary disease	1.35	1.29	1.42	0*
Peptic ulcer	1.15	0.99	1.31	0.0910
Liver disease	1.22	1.08	1.35	0.0048*
Hemiplegia	1.05	0.66	1.44	0.7976
Renal disease	1.05	0.96	1.15	0.258
Cancer history	1.12	1.04	1.21	0.0093*
Leukemia	1.11	0.75	1.46	0.5785
Lymphoma	0.99	0.66	1.32	0.9323
AIDS/HIV	0.74	-0.84	2.32	0.7088

*Indicates p-value<0.05

Table 6. The use of oral anticoagulants after diagnosis of atrial fibrillation

	Atrial fibrillation n (%)	Control n (%)	P-value
Vitamin K antagonist			
Acenocoumarol	272 (2.83)	75 (0.27)	<0.05*
Phenprocoumon	1548 (16.10)	425 (1.51)	<0.05*
Warfarin	1155 (12.00)	253 (0.90)	<0.05*
Direct oral anticoagulants			
Apixaban	2932 (30.50)	442 (1.57)	<0.05*
Dabigatran	1034 (10.70)	143 (0.51)	<0.05*
Rivaroxaban	2363 (24.60)	508 (1.81)	<0.05*
Edoxaban	17 (0.18)	6 (0.02)	0.297

*Indicates p-value<0.05

Table 7. Evolution of prescriptions of oral anticoagulants after the diagnosis of atrial fibrillation

	Annual percent change APC (%)	Average annual percent change AAPC (%)
CHA_2DS_2-VASc score = 0		-2.0*
2002-2007	2.05	
2007-20022	-3.43*	
CHA_2DS_2-VASc score = 1		0.7
2002-2007	8.91*	
2007-2010	-5.60	
2010-2013	14,53	
2013-2022	-3.69*	
CHA_2DS_2-VASc score ≥2		4.7*
2002-2015	6.65*	
2015-2022	-1.00	
All		3.4*

*Indicates p-value<0.05

Table 8. Univariate analysis: predictors of a cerebrovascular event after diagnosis of atrial fibrillation

	Univariate HR	95% CI low	95% CI high	P-value
Age (per year increase)	0.99	0.98	1.01	0.4429
Age group,				
65-74 years	1.55	1.01	2.08	0.1106
75-84 years	1.25	0.72	1.79	0.4058
>85 years	0.81	-0.05	1.67	0.6301
Sex (men)	1.23	0.85	1.61	0.2863
CHA_2DS_2-VASc score (per point increase)	1.38	1.22	1.54	0.0001*
Comorbidity				
Congestive heart failure	0.33	-1.07	1.73	0.1225
Hypertension	1.50	1.12	1.89	0.0385*
Diabetes Mellitus	1.86	1.38	2.33	0.0110*
Peripheral vascular disease	1.63	0.90	2.36	0.1923
Chronic pulmonary disease	0.98	0.45	1.50	0.9380
Peptic ulcer	1.03	0.31	1.75	0.9301
Liver disease	1.73	0.83	2.63	0.2322
Cancer History	1.84	1.07	2.61	0.1225
Myocardial infarction	1.55	0.89	2.20	0.1944

*Indicates p-value<0.05

Table 9. Multivariate analysis: predictors of a cerebrovascular event after diagnosis of atrial fibrillation

	Multivariate HR	95% CI low	95% CI high	P-value
Age (per year increase)	0,99	0.98	1.01	0.4790
Sex (men)	1,19	0.78	1.59	0.4113
Congestive heart failure	0,27	-1.14	1.69	0.0729
Hypertension	1,45	1.05	1.85	0.0660
Diabetes Mellitus	1,86	1.37	2.36	0.0140*
Peripheral vascular disease	1,46	0.71	2.22	0.3215
Chronic pulmonary disease	0,85	0.32	1.39	0.5645
Peptic ulcer	0,92	0.18	1.66	0.8289
Liver disease	1,46	0.54	2.37	0.4200
Cancer History	1,96	1.18	2.75	0.0925
Myocardial infarction	1,58	0.92	2.25	0.1775

*Indicates p-value<0.05

Figure 1. Incidence of atrial fibrillation (AF) by age category

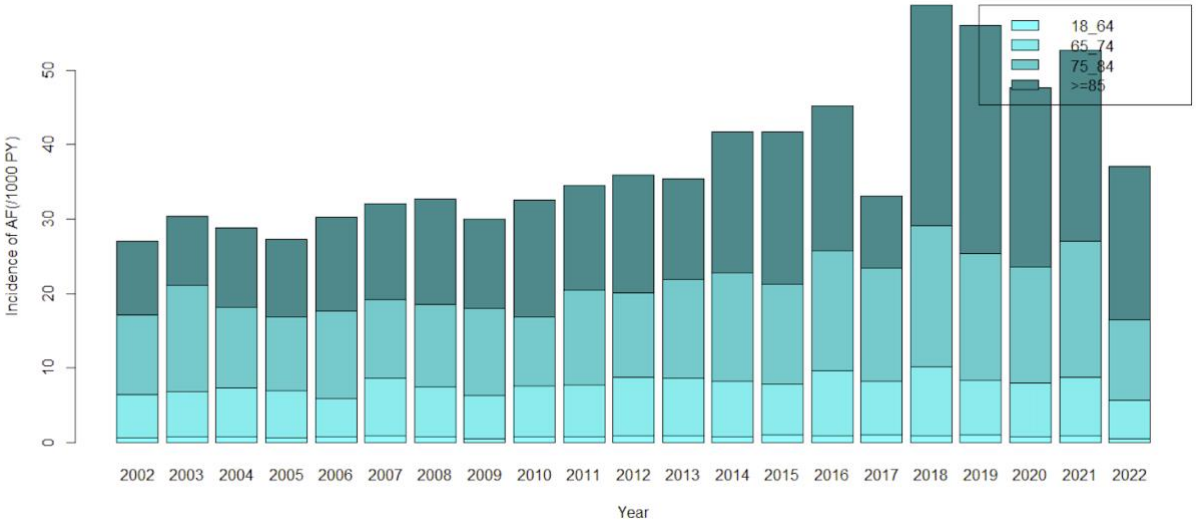
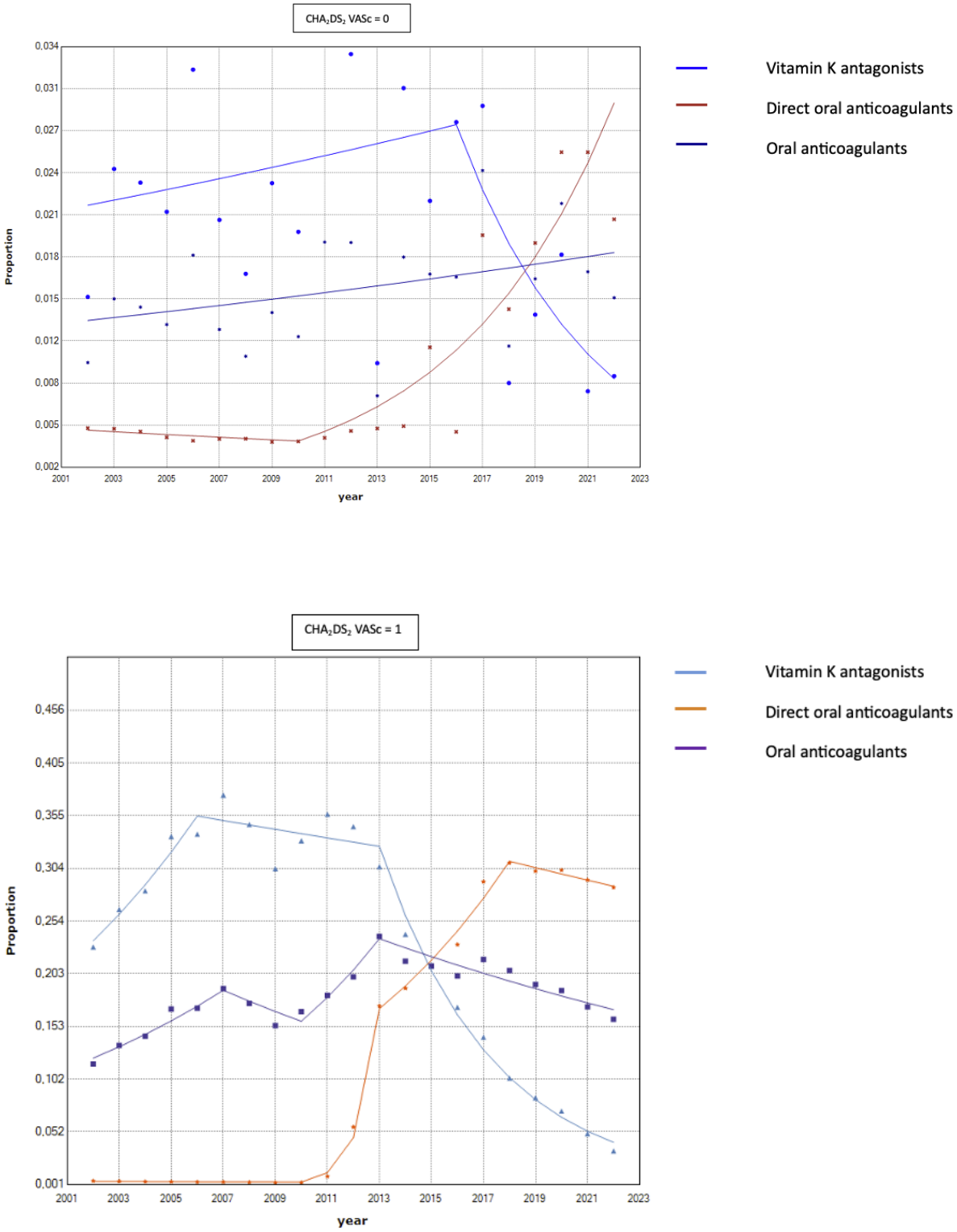


Figure 2. The evolution of oral anticoagulants prescriptions after a diagnosis of atrial fibrillation by CHA_2DS_2 VASc



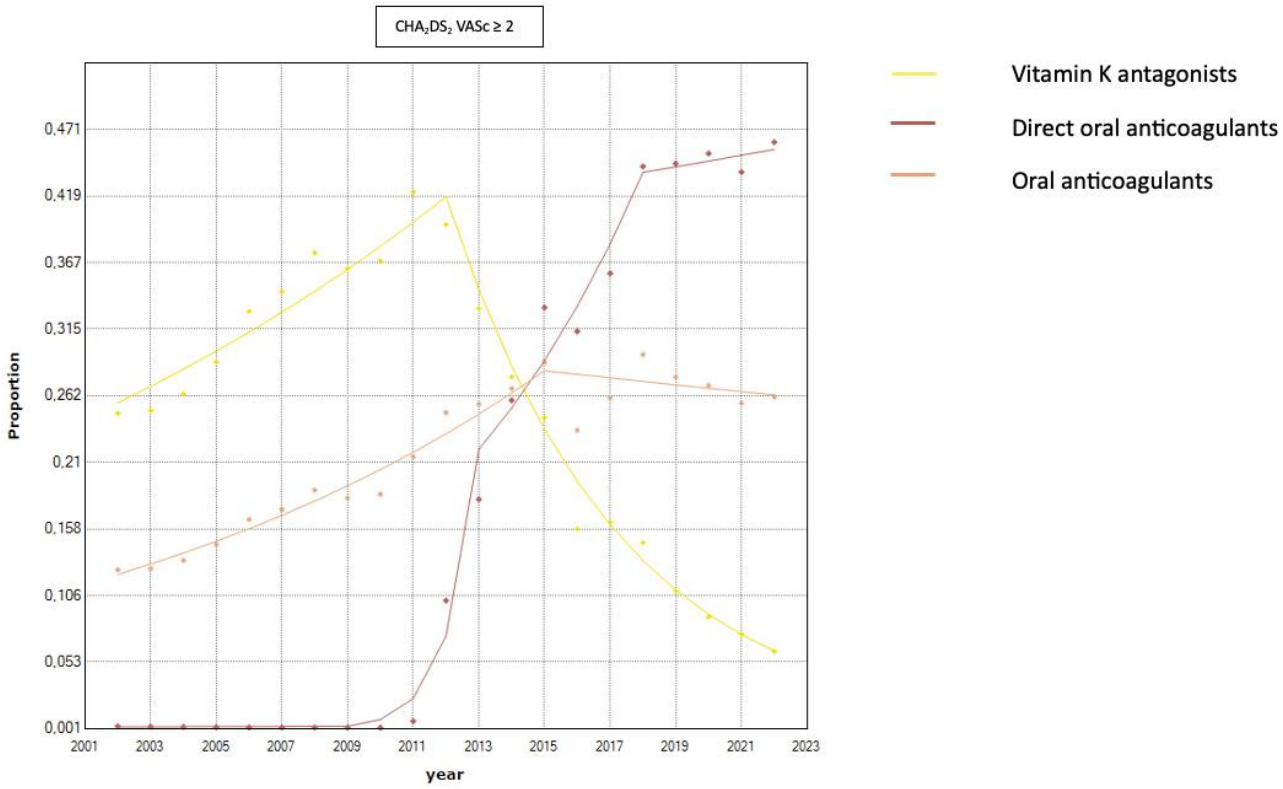
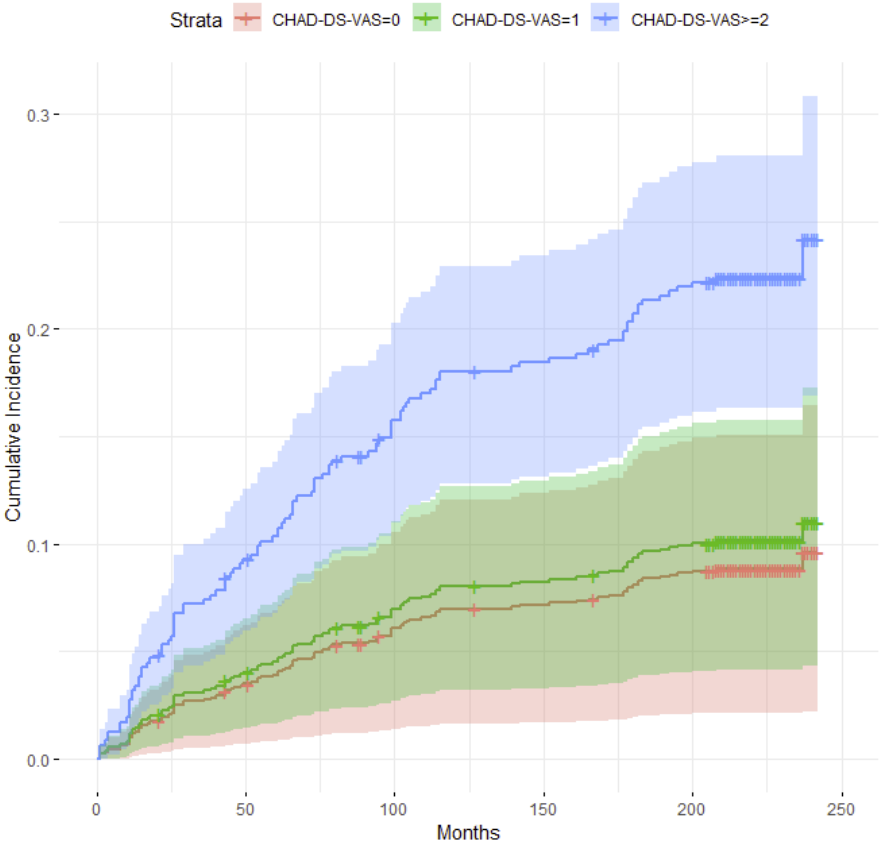


Figure 3. Time-to-event analysis of a cerebrovascular event after atrial fibrillation.



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