The correlation between atrial fibrillation and multimorbidity in general practice: a registry-based retrospective cohort study

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De correlatie tussen atriumfibrillatie en multimorbiditeit in de

huisartsenpraktijk: een databankgebaseerde retrospectieve cohort studie.

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Context: Atriumfibrillatie (AF) is de meest frequente chronische hartritmestoornis. AF kent reeds een hoge prevalentie en verwacht wordt dat deze prevalentie de komende decades nog sterk zal stijgen. Oudere patiënten met AF hebben vaker multimorbiditeit en een verhoogd risico op CVA vergeleken met patiënten zonder deze aandoening. Daarom is kennis van de interacties tussen comorbiditeit en AF erg belangrijk in het organiseren van een goed anticoagulatie-beleid. Als huisarts spelen we een sleutelrol in de patiëntgerichte zorg voor oudere AF patiënten.

Onderzoeksvraag: Wat is de epidemiologie van AF in België? Bestaat er een correlatie tussen AF, comorbiditeit en CVA?

Methode: We voerden een retrospectieve cohort studie uit op Intego data van 1 januari 2002 tot 31 december 2011. Intego is een databank bestaande uit gecodeerde patiënt-informatie van 97 huisartsen uit 55 praktijken verspreid in Vlaanderen. We includeerden 1830 patiënten die in 2002 60 jaar of ouder waren en AF ontwikkelen tussen 2002 en 2011, evenals 6622 gematchte controle patiënten. De resultaten werden nadien met recente literatuurgegevens vergeleken.

Resultaten: AF is met een prevalentie van 6.4% in 2011 een zeer prevalente aandoening bij zestigplussers. We observeerden een stijgende trend in de AF prevalentie. Patiënten met AF hadden significant meer comorbiditeit, 92% van hen hadden een mCCI ≥ 3 (gemodificeerde Charlson Comorbiditeits Index), en multimorbiditeit was significant gecorreleerd met het risico op CVA. Binnen ons tienjarig tijdsinterval kregen 9.8% van de AF patiënten een CVA. We stelden in vergelijking met de richtlijnen zowel onder- als over-anticoagulatie vast bij AF patiënten. Een hoog risico op CVA ($CHADS_2 \geq 2$) was aanwezig bij 48.7% van de AF patiënten maar slechts 49.7% van hen kregen anticoagulatie-therapie in de 6 maanden na de diagnose van AF. Daartegenover staat dat 51% van de patiënten met een laag CVA risico ($CHADS_2 = 0$) toch anticoagulatie kregen.

Conclusie: AF kent een hoge prevalentie bij oudere patiënten in de huisartsenpraktijk. AF en CVA zijn significant gecorreleerd met comorbiditeit. We observeerden een discrepantie tussen de richtlijnen en de huisartsenpraktijk wat betreft anticoagulantiagebruik ter preventie van CVA bij AF patiënten. Gezien multimorbiditeit hier een rol lijkt in te spelen is er bijkomend, kwalitatief onderzoek nodig om de correlatie tussen AF, comorbiditeit en CVA te verduidelijken.

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The correlation between atrial fibrillation and multimorbidity in general practice: a registry-based retrospective cohort study

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ABSTRACT

Objectives: To investigate the epidemiology of atrial fibrillation (AF) and anticoagulation-use in Flanders, Belgium, taking multimorbidity into account. Secondly, to explore the correlation between atrial fibrillation, comorbidity and stroke during a 10 year time interval.

Design: Retrospective cohort study on Intego data of a 10 year time interval from January 1st 2002 to December 31st 2011.

Setting: Primary registration network with 97 general practitioners working in 55 practices sending routinely collected patient data.

Participants: From the database, all patients aged 60 years and older in 2002 who developed atrial fibrillation between 2002 and 2011 were selected, as well as a group of control patients.

Main outcome measures: Prescription of anticoagulation treatment, stroke.

Results: AF is with a prevalence of 6.4% in 2011 a highly prevalent condition in patients of 60 years and older. An upward trend in AF prevalence was observed. In total 1830 AF-patients and 6622 control patients were included in the cohort study. AF patients had significantly more comorbidities, as 92% of AF patients had a mCCI (modified Charlson Comorbidity Index) ≥ 3, and multimorbidity was significantly correlated with stroke risk. Within a 10 year time interval 9.8% of AF patients developed a stroke. There was both an under- and overuse of anticoagulation in AF patients when compared with guidelines: 48.7% of the AF patients were at high stroke risk ($CHADS_2 \geq 2$) and only 49.7% of them received anticoagulation in the first six months after diagnosis, whereas 51% of patients at low risk ($CHADS_2 = 0$) were anticoagulated.

Conclusions: AF is highly prevalent in older primary care patients and is significantly correlated with comorbidities, as is stroke risk in AF patients.

There is still a discrepancy between the guidelines and the clinical practice in anticoagulation use for stroke prevention in older AF patients. As multimorbidity seems to play a role herein, further qualitative research needs to be done about the correlation between atrial fibrillation, comorbidity and stroke.

What this paper adds

What is already known on this subject?

Patients with AF typically have multiple comorbidities and have an elevated risk of stroke compared to individuals without the condition. However, very few studies assessed the correlation between atrial fibrillation, multimorbidity and stroke risk in older patients.

What this study adds

This registry-based retrospective cohort study is the first comprehensive study about atrial fibrillation in older primary care patients taking multimorbidity into account. We explored the discrepancy between the guidelines and clinical practice in anticoagulation use for stroke prevention in AF patients. The presence of comorbidity is found to be significantly correlated with AF development and stroke risk in AF patients.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Prevalence of AF is known to increase with age; more than three-quarters of the AF-patients is older than 65 years.[1] AF currently affects more than 8.8 million adults in the European Union. This number is expected to double within the next 50 years as the population rapidly ages.[2] Patients with AF typically have multiple comorbidities and have an elevated risk of cerebro-vascular events compared to individuals without the condition.[3] As a result, knowledge of the interactions between comorbidity and AF, as well as a good anticoagulation management are extremely important both for medical and economic reasons. General practitioners (GPs) play a key-role in the patient-centered care for older patients with AF and concomitant conditions.

Oral anticoagulation treatment for high stroke risk patients with AF has demonstrated to be effective in reducing the risk for stroke.[4] The stroke risk is assessed using the $CHADS_2$ and CHA_2DS_2-VASc scores, validated stratification schemes wherein the presence of certain comorbidities determines the need for anticoagulation.[5,6] Since increasing age itself is an important risk factor for stroke, both Belgian and international guidelines recommend using these scoring-systems also for older patients.[7,8,9]

Nevertheless, multiple papers suggest there is genuine under-use of anticoagulation in elderly patients in the primary care setting, even when correcting for the increased risk of bleeding in this age-group.[10,11] The increasing prevalence of multimorbidity in primary care complicates treatment.[12] To date, very few studies assessed the link between atrial fibrillation, multimorbidity and stroke risk in older patients.

Therefore, this registry-based retrospective cohort study investigated the epidemiology of AF and anticoagulation-use in Flanders, Belgium, taking multimorbidity into account. Secondly, the correlation between atrial fibrillation, comorbidity and stroke was explored during a 10 year time interval.

Methodology

Study design

Data were obtained from Intego, a Flemish general practice-based morbidity registration network at the Department of General Practice at the University of Leuven. Ninety-seven general practitioners (GPs), all using the medical software program Medidoc, collaborate in the Intego project. These 97 GPs work in 55 practices evenly spread over Flanders, Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer-generated keywords internally linked to codes. Using specially framed extraction software, new data were coded and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

Intego started to collect data in 1994 but in the present retrospective cohort study data of a 10 year time interval from January 1st 2002 to December 31st 2011 were used.

Study population

In 2002 20301 patients registered in the Intego database were aged 60 years and older and had at least one contact with their general practitioner. Of these 1068 were already

diagnosed with AF before 2002 and were therefore excluded from our study. Inclusion criteria for the cases were a reported first diagnosis of atrial fibrillation (ICPC - code K78) between January 1st 2002 and December 31st 2011. In total 1830 patients were diagnosed with AF. All participants were followed till the last contact date in the Intego registry or till December 31st 2011, whichever came first.

Each AF patient was matched with 3 or 4 control patients, bringing the number of controls up to 6622. These patients were still in the Intego database at the moment of the AF diagnosis in the case, belonged to the same age stratum in 2002 (60 – 69, 70 – 79 or ≥ 80 years old), had the same gender and originated from the same GP practice but were not diagnosed with AF during the follow-up period.

Clinical characteristics

Outcome variables

The first outcome variable was the diagnosis of AF, registered in the patient file by the GP. The date of the diagnosis of AF in the case served as the baseline date for that case and its matched controls. A second outcome variable was the diagnosis of Transient Ischaemic Attack (TIA) (ICPC – code K89) or Cerebro-Vascular Accident (CVA) (ICPC – code K90), registered by the GP.

The internationally used definition of TIA changed in 2009, during our follow-up period. Previously emphasizing the temporary nature of neurologic symptoms (< 24 hours), now a TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction.[19] It is unclear which of both definitions GPs used when coding TIA in their EMD. Therefore we used 'stroke' for both TIA and CVA in this paper.

Stroke Risk

$CHADS_2$ and CHA_2DS_2-VASc scores were calculated to determine the stroke risk of the included patients. The $CHADS_2$ score assigns 1 point for heart failure, hypertension, age ≥ 75 years, and diabetes mellitus and 2 points for prior stroke. The CHA_2DS_2-VASc score includes three additional risk factors for ischemic stroke: age 65–74 years, female sex, and vascular disease, the latter defined as previous myocardial infarction or peripheral arterial disease.[5,6]

Comorbidity

The Charlson Comorbidity Index (CCI) includes 19 chronic diseases which are weighted based on their association with mortality.[13] The presence of the following diagnoses was collected: diabetes mellitus, a history of myocardial infarction, heart failure, a history of transient ischaemic attack or cerebrovascular accident, peripheral arterial illness, chronic pulmonary disease, a history of peptic ulcer, dementia, liver disease, hemiplegia, a history of cancer, a history of leukaemia, a history of lymphoma and AIDS. Connective tissue disease could not be reliably assessed from the registry and the difference between cancers with or without metastasis, diabetes with or without end organ failure and mild or moderate to severe liver disease could not be made. Consequently all cancers were assigned the same score, all diabetics were assigned the same score and all patients with liver disease were assigned the same score. Therefore we used a modified CCI (mCCI) in all further analyses.

The mCCI at the time of diagnosis of atrial fibrillation was calculated for each case and its controls. mCCI was not available for 87 AF patients because no creatinine levels were available in the database. In addition to the mCCI diagnoses of hypertension and valvular heart disease were extracted at baseline.

Pharmacotherapy

The prescription of cardiovascular medication (ATC-coded) including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium antagonists, diuretics, digitalis and antiarrhythmic drugs was extracted for every study participant at baseline and 6 months after the diagnosis of AF for the cases.

The prescription of antithrombotic therapy was registered for cases in the first 6 months after the diagnosis of AF (ATC-coded: Heparin, Acetylsalicylic acid, Thienopyridine, Dipyridamol, Vitamin K antagonists). Throughout this paper we used the term 'anticoagulation' for both oral anticoagulants (Vitamin K antagonists) and subcutaneous heparin treatment. When assessing whether patients were receiving anticoagulation treatment after the diagnosis of AF, we used a 6 month time frame as there could be a doctor-delay in registering treatment changes.

Data analysis

Continuous data are presented as the mean and standard deviation (SD). Categorical data are presented as numbers and frequencies. Comparisons between cases and controls were performed using the independent samples t test or the χ^2 test for categorical data.

We calculated the prevalence and incidence of atrial fibrillation each year in the yearly contact group, these are the patients of 60 years and older who had at least one contact with their GP that year.

The correlation between the presentation of novel atrial fibrillation and comorbidity was explored by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) using bivariate and multivariable logistic regression analyses adjusting for age, gender and cardiovascular medication at the moment of diagnosis. Two different models were used; one with the mCCI and one with the different comorbidities of the mCCI without the overall index.

The risk for stroke after the diagnosis of atrial fibrillation based on the presence of comorbidity was calculated using a Cox proportional hazards model and adjusted for age and gender. Two different models were used: one with the mCCI and $CHADS_2$ or CHA_2DS_2-VASc score and one with the different comorbidities without the overall score.

The correlation between the prescription of anticoagulation in the first six months after the diagnosis of atrial fibrillation and comorbidity was investigated using bivariate and multivariable logistic regression analyses adjusting for age, gender and cardiovascular medication prescribed in the six months after the diagnosis of atrial fibrillation. Two models were used as previously described. Afterwards individual patient profiles were investigated to explore further the relationship between the prescription of anticoagulation and the presentation of stroke. For those who received oral anticoagulation treatment (vitamin K antagonists), we checked the INR values to see whether they were within a therapeutic range (INR 2 – 3.5). Patients who had a first diagnosis of AF at the same time as a stroke were excluded from certain analyses since there was no time to anticoagulate them before the event.

In order to avoid co-linearity, the correlation coefficients between all covariates were calculated. In case of co-linearity (r-value > 0.90), only one of the two covariates was considered in the multivariable model.

The statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Epidemiology

The yearly prevalence of AF in the Intego database in patients aged 60 years or older from 2002 till 2011 is shown in Figure 1. An upward trend was observed with an overall prevalence of 5.3% in 2002 compared to 6.4% in 2011. The prevalence of atrial fibrillation rises with age, being more prevalent in octogenarians (10.1% in 2002; 11.8% in 2011), than in patients aged 60-69 years (2.5% in 2002; 3.0% in 2011).

The yearly incidence of atrial fibrillation in patients aged 60 years or older is also shown in figure 1, expressed per 1000 person years. The overall incidence seemed to be slightly rising from 6.1/1000 patient years in 2002 to 7.8/1000 in 2011. This upward trend was not present in the youngest patients. The AF incidence was highest in the oldest group of patients.

Our cohort included 8452 patients of whom 1830 patients were diagnosed with atrial fibrillation between 2002 and 2011. The mean age was 77 years and 49.1% of our patients were men, as shown in Table 1. The average control patient was slightly younger than the average AF patient at the moment of the AF diagnosis.

Comorbidity

Cases differed significantly from controls for several parameters such as the prescription of cardiovascular medication and the presence of comorbidity (Table 1). Patients with AF had a significantly higher mCCI. More specifically, AF patients presented more often with a history of myocardial infarction, heart failure, peripheral vascular disease, history of stroke, diabetes and renal disease. The prevalence of hypertension and valvular heart disease was also higher in patients who developed atrial fibrillation compared to the control group. A total of 92% of the AF patients had a mCCI of 3 or more.

Increasing age and diabetes seemed to be predictors for developing AF in the bivariate logistic regression analysis shown in Table 2. However, when correcting for cardiovascular

medication prescription and comorbidity in a multivariable analysis, the correlation between age, diabetes and AF was not longer significant. The mCCI was an independent predictor for AF. In the model without the overall index a history of myocardial infarction, heart failure, stroke, renal disease and heart valve disease showed to be independent predictors of AF. In the multivariable analysis hypertension was not a significant predictor but hypertension treatment with β blockers, calcium channel blockers and ACE-inhibitors was associated with a higher AF risk.

The analyses were also made with the patients split into 3 age strata based on their age in 2002 (Table 3). A history of heart failure and valvular heart disease were independently correlated with AF in all age strata. AF patients aged 60 – 79 years were prescribed significantly more β blockers than the controls. In the patients aged 80 years and older a stronger and independent correlation was observed between AF and ACE-inhibitor prescription, diabetes, renal disease, history of tumor and hypertension compared to the younger patients. However, the presence of diabetes and a history of tumor were negatively correlated with the AF diagnosis.

Stroke

A stroke was diagnosed in 178 of the 1830 AF patients (9.7%) during the 10 year time frame. Stroke was the first presentation of AF in 46 Patients (26%). In the first 6 months after the diagnosis of AF 78 patients (44%) developed a stroke.

A Cox regression analysis was performed to explore the predictors of stroke after the diagnosis of atrial fibrillation (Table 5). Increasing age was in both the bivariate and the multivariable analysis a predictor for a higher stroke incidence in AF patients (HR 1.05 (95% CI 1.03 - 1.07)). Both $CHADS_2$ and CHA_2DS_2-VASc scores were strong predictors for stroke (HR 1.5 (95% CI 1.3 – 1.7) and HR 1.4 (95% CI 1.2 – 1.6), respectively). AF patients who had had a stroke in the past were at a much greater risk for a recurrent ischaemic cerebro-

vascular event (HR 5.2 (95% CI 3.8 - 7.2)). An independent correlation was also found between renal disease and stroke after the diagnosis of AF (HR 1.3 (95% CI 1.1 - 1.6)).

Anticoagulation treatment

The determinants of receiving anticoagulation therapy within the first 6 months after the diagnosis of atrial fibrillation are shown in Table 4. Overall, 49% (n = 895) of AF patients in our study were receiving anticoagulation within 6 months after AF diagnosis. When split into age groups, 49% of patients aged 60 – 69 years were prescribed anticoagulation (n = 140), 52% of patients aged 70 – 79 years (n = 425) and 45% of patients aged 80 years and older (n = 330). Age was a significant determinant in a bivariate model (less anticoagulation with increasing age), but not in the multivariable model.

Male AF patients were more frequently receiving anticoagulation than women (OR 1.5 (95% CI 1.2 – 1.8)). In total 53% of men with AF were prescribed anticoagulation treatment, compared to 45% of female AF patients.

When patients were prescribed other cardiovascular medication such as digitalis, antiarrhythmic drugs and antihypertensive drugs, they were more likely to receive anticoagulation. However, AF patients with more comorbidity, reflected by a higher mCCI, received less anticoagulation therapy (OR 0.90 (95% CI 0.83 - 0.97)). Patients suffering from dementia were less anticoagulated, as were patients with a history of peptic ulcer or a history of tumor. Previous stroke did not significantly alter the anticoagulation frequency (OR 1.2 (95% CI 0.86 – 1.6)). However, occurrence of stroke in the first 6 months after diagnosis of AF was a predictor to receive anticoagulation (OR 1.8 (95% CI 1.0 – 3.1)).

Of the AF patients in our study 15.6% had a $CHADS_2$ score of 0 (n = 285); 35.7% scored 1 (n = 654) so 48.7% had a $CHADS_2$ score of 2 or more (n = 891). Assessed with the CHA_2DS_2-VASc score, 1 % of the AF patients scored 0 (n = 19); 8.6% scored 1 (n = 157) and 90.4% had a score of 2 or more (n = 1654). In total 51% of the patients with a $CHADS_2 = 0$

(n = 146) and 58% with a CHA_2DS_2-VASc score = 0 (n = 11) did receive anticoagulation. In patients scoring 1 on the $CHADS_2$, 47% was anticoagulated (n = 306), as was 52% with CHA_2DS_2-VASc score = 1 (n = 81). When scoring $\geq$ 2 on the $CHADS_2$, 49.7% of patients was prescribed anticoagulation (n = 443), as was 48.5% with CHA_2DS_2-VASc score $\geq$ 2 (n = 803). Overall, there was no significant correlation between the $CHADS_2$ (*P* = 0.079) or CHA_2DS_2-VASc score (P = 0.086) and receiving anticoagulation after AF diagnosis, although there was a positive trend.

Of the 132 patients who developed a stroke during the follow up period 34 (25.8%) were taking anticoagulation therapy at the time of their stroke (Figure 2). Of these 15 were within a therapeutic INR range (2 – 3.5) at the time of the last blood test before the stroke, 13 were controlled sub-optimally (INR < 2), whereas 3 were over-coagulated (INR > 3.5). For 3 patients receiving anticoagulation after the diagnosis of AF no INR values were available. At the time of their stroke, 98 patients were not receiving anticoagulation. Of these 14 (14.3%) were prescribed anticoagulation after their stroke, whereas 84 AF patients remained without treatment.

Discussion

Epidemiology

The prevalence of AF in our study population is comparable to the results of the Dutch Rotterdam Study, a population-based prospective cohort study between 1990 and 2000 in patients aged 55 years and older.[1] They calculated an overall prevalence of AF of 5.5% whereas our overall prevalence in 2002 was 5.3%. The overall incidence in the Rotterdam-population was 9.9/1000 patient years, which was higher than the incidence in our population. Both studies found a steep increase in both the prevalence and incidence with age.

An upward trend was observed in the AF prevalence between 2001 and 2011. A study on the Global Burden of Disease 2010 data confirms this modest upward trend within the same time frame.[26] Several papers predict a more dramatic escalation in the AF burden in the coming decades, both from a health care and whole-societal perspective.[2, 25, 27]

Comorbidity

The results of our study exceed previous findings about the high comorbidity index in patients with AF. The National Health and Wellness Survey data[3] from 2009 showed 79.9% of American AF patients had a CCI of 0–2 and 20.5% had scores ≥ 3, compared to 8% and 92% respectively in our population. However, with a mean age of 64.9 years, their population was younger than our study population, which might explain the higher burden of comorbidities in our study. Also their study was based on self-reported, and thus possibly under-reported data from an internet based survey, which might have excluded less computer-literate individuals, whereas our study was based on data registered by GPs, also including the oldest and sickest patients. However, when estimating stroke risk with $CHADS_2$ scores, the findings of both studies were comparable.

When correcting for cardiovascular medication prescription and comorbidity, the correlation between increasing age and AF was not significant in our population, in contrary

to very recent statistical updates of the AHA.[14] However, similar to their study, hypertension treatment, heart failure, myocardial infarction, valvular heart disease and renal disease were predictors of increased risk of new-onset AF. The correlation between AF and comorbidity is existing even in the oldest patients. Multimorbidity in elderly patients seems to influence the AF risk more than increasing age itself. The health burden carried by patients often extends far beyond atrial fibrillation, and specifically does so in older persons.

In our study population, diabetes mellitus was significantly more common in the AF-group than in the control group. However, with the multivariable analysis no significant correlation between diabetes and AF was found. Many epidemiologic studies have examined the atrial fibrillation risk in relation to diabetes or elevated blood glucose, with conflicting results. A large meta-analysis found an overall 34% increase in risk of AF after correcting for presence of publication bias[15]. However, they stated themselves that this number may be an overestimate of the real association between diabetes and AF because of the possibility of confounding. Our study, on the other hand, suggested that it is more important to consider the combination of different comorbidities in a patient to predict AF development, than to look specifically for certain conditions such as diabetes.

Stroke

Almost 10% of AF patients developed a stroke during the 10 year time interval, emphasizing the importance of the thrombo-embolic risk. Although a history of stroke before the diagnosis of AF did not significantly alter the anticoagulation frequency, it was identified as a major risk factor for recurrent stroke. This is similar to the results of a systematic review published by 'The Stroke Risk in Atrial Fibrillation Working Group'.[18] Prior stroke proved to be the most powerful risk factor and reliably confers a high stroke risk in their study. They also found advancing age, hypertension and diabetes to be independent risk factors for stroke in AF patients. In our study advancing age was also an independent risk factor for stroke, but

hypertension and diabetes were not. Both $CHADS_2$ and CHA_2DS_2-VASc scores were confirmed to be strong predictors for stroke in our AF patients. As both score-systems take previous stroke and age into account, parameters that have shown to be important individual predictors for stroke development in our study, use of these scores is mandatory in daily primary care practice. It might also be important to be extra careful with AF patients who have concomitant kidney problems, as our study observed a high stroke risk in persons with renal disease.

Of the AF patients who developed a stroke in our study 26% did so at the time of the first diagnosis of AF. Although it is possible that they developed a stroke immediately after the start of their heart rhythm disorder, there might also be a doctor-delay in diagnosing heart rhythm problems in primary care patients. Other studies have shown that opportunistic pulse taking is the preferred method of screening and could be important in the prevention of stroke.[20]

Anticoagulation treatment

Several studies reported underuse of anticoagulation therapy in older patients and increasing age is reported as a barrier to start anticoagulation.[1, 10, 11] Overall, 49 % of the included AF patients were receiving anticoagulation in the 6 months after the diagnosis of atrial fibrillation. However, the anticoagulation was not always continued until the censor date or the event. A study in the UK based on the General Practice Research Database (GPRD) data from 2000 until 2009 found that 57% of patients aged 60–69 years, 55% of patients aged 70–79 years and 32% of patients aged 80 years and older received warfarine.[10] In the younger age groups, our patients were less anticoagulated than the GPRD patients, however, in the patients aged 80 years and older our GPs prescribed a lot more anticoagulants. When corrected for comorbidity, age was not a significant determinant of (not) receiving anticoagulation, but is a predictor for higher stroke incidence in our population.

This finding is according to the guidelines, who state that even for the very elderly the same risk-benefit analysis should be made to determine the need for anticoagulation.[7-9, 21]

In our study 51% of the AF patients who developed a stroke after the diagnosis of AF did not receive anticoagulation in the first 6 months after AF diagnosis. Of the patients who developed a stroke and did receive anticoagulation treatment, more than half was not within a therapeutic INR range at the time of their stroke. Overall, there seems to be a large scope for improvement of the anticoagulation management. Literature review has identified both patient- and physician-related barriers to anticoagulation prescription.[23]

We observed both an over-treatment in low stroke risk AF patients and an under-treatment in patients at high stroke risk when compared to the guidelines. $CHADS_2$ and CHA_2DS_2-VASc scores were strong predictors for stroke in our AF patients but these scores were not significantly correlated to anticoagulation prescription. Of the patients at low risk for stroke, scoring 0 on the $CHADS_2$ score or CHA_2DS_2-VASc score, 51% and 58% respectively did receive anticoagulation. The same trend is seen in other studies such as the ORBIT-AF study.[22] Although it is possible that these patients may have been anticoagulated for conditions other than AF, it is unlikely that these conditions alone would account for the relatively high anticoagulation rates. GPs may be anticoagulating these patients simply because they have AF, regardless of their low stroke risk. On the contrary, only 49.7% of the individuals at high risk for stroke ($CHADS_2 \geq 2$) were receiving anticoagulation. This is comparable to findings of the NHWS study, where only 48% of individuals at high risk for stroke ($CHADS_2 \geq 2$) reported use of anticoagulation therapy.[3] A study in GP practices in England reported 54.7% of the patients with a $CHADS_2 \geq 2$ to be taking anticoagulation.[17] It is possible that GPs are not aware of how infrequently they prescribe anticoagulants. Therefore it is important that quality of care audits can easily be done with their medical software program.

Another reason for under-anticoagulation could be the bleeding risk of an AF patient, as perceived by the GP. Since we were not able to calculate a bleeding risk score we could not estimate whether bleeding risk was correctly taken into account by our Intego GPs. Patients with a history of peptic ulcer or a history of tumor were receiving less anticoagulation, probably due to a high perceived bleeding risk. Patients suffering from dementia were also less anticoagulated, fear for poor compliance and risk for falls might play a role herein.

The perceived thrombo-embolic risk of the AF patients could be a physician related barrier to anticoagulation prescription. For example, male AF patients in our Intego population are more frequently receiving anticoagulants than women, even when corrected for confounders. This finding is consistent with results from other studies, such as the study on the GPRD mentioned above.[10] Gender inequalities have been observed in use of therapies in other areas of cardiovascular medicine and have been attributed to a possible perceived lower risk of cardiovascular disease in women compared with men, leading to under-recording of risk factors and lower rates of prophylactic treatment in women. [16] However, female gender is a component of the CHA_2DS_2-VASc score because epidemiologic data proves that women have an increased thrombo-embolic risk compared to men.[6] Therefore GPs should change their perception about the stroke risk in women with AF and more carefully assess their need for anticoagulation.

The increasing prevalence of multimorbidity in primary care could be another complicating factor, possibly leading to clinical uncertainty about therapeutic decisions. AF patients with more comorbidity, reflected by a higher mCCI, did receive less anticoagulation therapy. However, when patients are taking other cardiovascular medication such as digitalis, antiarrhythmic drugs and antihypertensive drugs, they are more likely to be prescribed anticoagulants.

A lot of research about anticoagulation in AF patients has already been done and clinically useful guidelines are developed. A thorough knowledge of the guidelines by the GPs is important to make evidence-based decisions. Currently, evidence based medicine is the gold standard in primary care, and physicians are well-trained to search for and follow guidelines. However, our study proves that there is still a discrepancy between the guidelines and the clinical practice in stroke prevention in older AF patients. It is important to further clarify the barriers that GPs experience when treating older AF patients. As multimorbidity seems to play a role in the therapeutic decision making process and in the risk for stroke, it is important to understand fully its impact. Therefore, more qualitative research, like focus group research or semi-structured interviews, needs to be done to further investigate attitudes of general practitioners in prescribing anticoagulants in AF patients with multimorbidity. Care plans should be designed and implemented according to the individual medical history, risk factors and needs of each patient. Primary care physicians are probably in the best position to take the key-role in managing the care for our older patients.

Strengths and limitations

A strong point of this paper is the inclusion of a large primary care population that is representative of the population in Flanders followed in primary care. The database contains all introduced diagnoses and most of the relevant clinical parameters. Due to the retrospective design there is a 10 year follow-up of the clinical and biological parameters. The data analyses with longitudinal models incorporate between-subject (case – control) and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions. Therefore, we were able to make the first comprehensive study about atrial fibrillation and multimorbidity in a primary care setting.

Limitations are the lack of mortality data and the lack of a creatinine value for 10% of the included patients. Due to database limitations data to calculate HASBLED-scores,

estimating the bleeding risk of an AF patient, were not available. Also, there are weaknesses inherent to an observational, retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up. Also because of the retrospective character, this study is able to formulate hypotheses, but unable to determine any causal relationship. Recently the anticoagulation-therapy options changed due to the introduction of the NOAC's (factor Xa inhibitors, thrombin inhibitors). These are not taken into account since these drugs were not yet available in Belgium before 2012 and our study is performed on data from 2002-2011.

Conclusion

Atrial fibrillation is, with a prevalence of 6,4% in 2011 in patients aged 60 years and older, a highly prevalent condition in elderly patients in primary care and a major risk factor for stroke. Due to ageing of our population AF prevalence is expected to rise in the coming decades, making preventative strategies to reduce the risk of AF within comprehensive health management programs increasingly important. Our study confirms the very high burden of comorbidities in AF patients. These conditions are predictors for both AF development and stroke risk in AF patients, and should thus be considered when making decisions about anticoagulation treatment. There is both an under- and overuse of anticoagulation in AF patients, possibly due to the multimorbidity of AF patients which is complicating treatment. Further qualitative research is needed to clarify the nature of this correlation and the barriers GPs experience when considering anticoagulation treatment. A better knowledge of these interactions will hopefully lead to a better preventive and curative management of the older patient's health.

Contributors VV and BV performed the analyses and wrote the manuscript. CT and SE extracted the data. FB is responsible for the study concept, design and acquisition of subjects and data. All authors participated in the interpretation of the data.

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Competing interests None.

Ethics approval The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

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Table 1 Description of the study population (n = 8452).

Variable	Atrial fibrillation (n = 1830)	Control (n = 6622)	*P* value*
Age (years), mean ± SD	77.5 ± 7.3	77.0 ± 7.2	0.006
Men, n (%)	900 (49.2)	3253 (49.1)	0.97
Cardiovascular medication before AF diagnosis n (%)	1005 (54.9)	2523 (38.1)	<0.001
Diuretic, n (%)	495 (27.0)	1198 (18.1)	<0.001
β blocker, n (%)	603 (33.0)	1357 (20.5)	<0.001
Calcium channel blocker, n (%)	303 (16.6)	674 (10.2)	<0.001
ACE-inhibitor, n (%)	340 (18.6)	756 (11.4)	<0.001
ARB, n (%)	172 (9.4)	440 (6.6)	<0.001
Comorbidity			
Charlson Comorbidity Index, mean ± SD	5 ± 2	4 ± 2	<0.001
Myocardial infarction, n (%)	235 (12.8)	513 (7.7)	<0.001
Heart failure, n (%)	214 (11.7)	260 (3.9)	<0.001
Peripheral vascular disease, n (%)	149 (8.1)	400 (6.0)	0.001
Stroke, n (%)	259 (14.2)	633 (9.6)	<0.001
Dementia, n (%)	62 (3.4)	242 (3.7)	0.59
Chronic pulmonary disease, n (%)	47 (2.6)	175 (2.6)	0.86
History of peptic ulcer, n (%)	150 (8.2)	472 (7.1)	0.12
Liver disease, n (%)	57 (3.1)	184 (2.8)	0.44
Diabetes, n (%)	319 (17.4)	884 (13.3)	<0.001
Hemiplegia, n (%)	30 (1.6)	71 (1.1)	0.048
Renal disease, n (%)	208 (11.9)	480 (8.1)	<0.001
History of tumor, n (%)	237 (13.0)	922 (13.9)	0.28
Leukemia, n (%)	5 (0.3)	24 (0.4)	0.56
Lymphoma, n (%)	7 (0.4)	33 (0.5)	0.52
Hypertension, n (%)	780 (42.6)	2213 (33.4)	<0.001
Valve disease, n (%)	181 (9.9)	235 (3.5)	<0.001

*, independent samples *t* test or Chi^2 test.

SD: standard deviation; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 2 Predictors of atrial fibrillation (logistic regression analysis, n = 8452).

Variable	Bivariate OR (95% CI)	*P* value	Multivariable	*P* value
Age (years)	1.01 (1.00 – 1.02)	0.006	1.00 (0.99 – 1.01)	0.71
Men	1.0 (0.90 – 1.1)	0.97	1.1 (0.95 – 1.2)	0.31
Cardiovascular medication				
Diuretic	1.7 (1.5 – 1.9)	<0.001	1.1 (0.96 – 1.3)	0.18
β blocker	1.9 (1.7 – 2.1)	<0.001	1.5 (1.4 – 1.7)	<0.001
Calcium channel blocker	1.8 (1.5 – 2.0)	<0.001	1.3 (1.1 – 1.5)	0.003
ACE-inhibitor	1.8 (1.5 – 2.0)	<0.001	1.2 (1.1 – 1.4)	0.010
ARB	1.5 (1.2 – 1.8)	<0.001	1.1 (0.87 – 1.3)	0.52
Comorbidity				
Charlson Comorbidity Index (per point increase)	1.10 (1.06 – 1.13)	<0.001	1.08 (1.04 – 1.12)*	<0.001
Myocardial infarction	1.8 (1.5 – 2.1)	<0.001	1.2 (1.0 – 1.4)	0.037
Heart failure	3.2 (2.7 – 3.9)	<0.001	2.4 (1.9 – 2.9)	<0.001
Peripheral vascular disease	1.4 (1.1 – 1.7)	0.001	1.0 (0.82 – 1.2)	0.90
Stroke	1.6 (1.3 – 1.8)	<0.001	1.3 (1.1 – 1.5)	0.006
Dementia	0.93 (0.70 – 1.2)	0.59	0.81 (0.60 – 1.1)	0.17
Chronic pulmonary disease	0.97 (0.70 – 1.3)	0.86	0.88 (0.62 – 1.2)	0.44
History of peptic ulcer	1.2 (0.96 – 1.4)	0.12	1.0 (0.86 – 1.3)	0.65
Liver disease	1.1 (0.83 – 1.5)	0.45	1.0 (0.74 – 1.4)	0.96
Diabetes	1.4 (1.2 – 1.6)	<0.001	1.0 (0.88 – 1.2)	0.78
Hemiplegia	1.5 (1.0 – 2.4)	0.050	1.2 (0.74 – 1.9)	0.49
Renal disease	1.2 (1.1 – 1.3)	<0.001	1.2 (1.1 – 1.3)	0.002
History of tumor	0.92 (0.79 – 1.1)	0.29	0.84 (0.71 – 0.99)	0.034
Leukemia	0.75 (0.29 – 2.0)	0.57	0.77 (0.29 – 2.1)	0.61
Lymphoma	0.77 (0.34 – 1.7)	0.52	0.84 (0.36 – 1.9)	0.68
Hypertension	1.5 (1.3 – 1.6)	<0.001	1.1 (1.0 – 1.3)	0.054
Valve disease	3.0 (2.4 – 3.6)	<0.001	2.2 (1.8 – 2.8)	<0.001

*, Adjusted for age, gender, diuretics intake, β blocker intake, calcium channel inhibitor intake, ACE inhibitor intake, ARB intake, arterial hypertension and valve

OR: odds ratio; CI: confidence interval; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; TIA: transient ischemic attack.

Multicollinearity was checked for.

Table 3 Correlation of atrial fibrillation and comorbidities (Logistic regression analysis, n = 8452)

Variable	60 – 69 years (2002)		70 – 79 years (2002)		≥ 80 years (2002)	
	Bivariate	Multivariable	Bivariate	Multivariable	Bivariate	Multivariable
Age (years)	1.0 (0.99 – 1.0)	1.0 (0.98 – 1.0)	1.0 (0.99 – 1.0)	1.0 (0.98 – 1.0)	1.0 (0.98 – 1.0)	1.0 (0.98 – 1.0)
Men	0.98 (0.82 – 1.2)	0.97 (0.80 – 1.2)	1.0 (0.87 – 1.2)	1.1 (0.89 – 1.3)	1.2 (0.94 – 1.6)	1.3 (0.97 – 1.7)[£]
Cardiovascular medication						
Diuretic	1.6 (1.3 – 2.0)[*]	1.0 (0.80 – 1.3)	2.0 (1.7 – 2.3)[*]	1.3 (1.1 – 1.6)[$]	1.2 (0.90 – 1.6)	0.79 (0.57 – 1.1)
β blocker	2.2 (1.8 – 2.6)[*]	1.8 (1.4 – 2.2)[*]	2.0 (1.7 – 2.3)[*]	1.5 (1.3 – 2.0)[*]	1.4 (1.0 – 1.9)[$]	1.2 (0.82 – 1.6)
Calcium channel blocker	1.7 (1.3 – 2.1)[*]	1.1 (0.86 – 1.5)	2.1 (1.7 – 2.6)[*]	1.6 (1.3 – 2.0)[*]	1.1 (0.79 – 1.7)	0.96 (0.63 – 1.4)
ACE-inhibitor	1.6 (1.3 – 2.1)[*]	1.1 (0.85 – 1.5)	1.8 (1.5 – 2.2)[*]	1.1 (0.90 – 1.4)	2.0 (1.4 – 2.8)[*]	1.7 (1.1 – 2.5)[$]
ARB	1.8 (1.4 – 2.3)[*]	1.2 (0.89 – 1.7)	1.4 (1.1 – 1.9)[$]	0.94 (0.69 – 1.3)	0.84 (0.47 – 1.5)	0.83 (0.44 – 1.5)
Comorbidity						
Charlson Comorbidity Index	1.2 (1.1 – 1.2)[*]	1.1 (1.0 – 1.2)[μ,$]	1.1 (1.1 – 1.2)[*]	1.1 (1.0 – 1.2)[μ,$]	1.0 (0.94 – 1.1)	0.98 (0.90 – 1.1)[μ]
Myocardial infarction	2.1 (1.6 – 2.8)[*]	1.4 (1.0 – 1.9)[£]	1.6 (1.3 – 2.1)[*]	1.1 (0.86 – 1.5)	1.5 (1.1 – 2.2)[$]	1.3 (0.89 – 1.9)
Heart failure	4.2 (2.7 – 6.6)[*]	2.7 (1.6 – 4.3)[*]	3.6 (2.7 – 4.8)[*]	2.7 (2.0 – 3.6)[*]	2.4 (1.7 – 3.3)[*]	2.0 (1.4 – 2.9)[*]
Peripheral vascular disease	1.6 (1.1 – 2.2)[$]	1.1 (0.75 – 1.6)	1.5 (1.1 – 1.9)[$]	0.98 (0.73 – 1.3)	0.97 (0.62 – 1.5)	0.78 (0.47 – 1.3)
Stroke	2.1 (1.6 – 2.9)[*]	1.7 (1.2 – 2.4)[*]	1.7 (1.4 – 2.1)[*]	1.4 (1.1 – 1.8)[$]	0.96 (0.71 – 1.3)	0.82 (0.58 – 1.2)
Dementia	0.95 (0.32 – 2.9)	1.1 (0.36 – 3.6)	0.90 (0.59 – 1.4)	0.82 (0.52 – 1.3)	0.83 (0.54 – 1.3)	0.79 (0.50 – 1.2)
Chronic pulmonary disease	1.3 (0.75 – 2.4)	1.4 (0.76 – 2.5)	0.90 (0.56 – 1.5)	0.76 (0.46 – 1.3)	0.71 (0.35 – 1.4)	0.66 (0.31 – 1.4)
History of peptic ulcer	1.1 (0.74 – 1.5)	0.91 (0.62 – 1.3)	1.3 (0.97 – 1.7)[£]	1.1 (0.83 – 1.5)	1.1 (0.69 – 1.6)	1.1 (0.68 – 1.6)
Liver disease	1.7 (1.1 – 2.6)[$]	1.5 (0.92 – 2.3)	0.88 (0.55 – 1.4)	0.77 (0.47 – 1.3)	0.60 (0.23 – 1.6)	0.55 (0.20 – 1.5)
Diabetes	1.8 (1.4 – 2.3)[*]	1.2 (0.95 – 1.6)	1.4 (1.2 – 1.7)[$]	1.1 (0.85 – 1.3)	0.67 (0.45 – 0.98)[£]	0.55 (0.36 – 0.84)[$]
Hemiplegia	1.6 (0.65 – 3.8)	0.78 (0.29 – 2.1)	1.5 (0.81 – 2.8)	1.2 (0.64 – 2.5)	1.4 (0.64 – 3.2)	1.6 (0.71 – 3.8)
Renal disease	1.3 (1.0 – 1.6)[$]	1.1 (0.87 – 1.4)	1.2 (1.1 – 1.4)[$]	1.1 (1.0 – 1.3)[£]	1.2 (1.0 – 1.4)[$]	1.2 (1.0 – 1.4)[$]
History of tumor	0.92 (0.70 – 1.2)	0.78 (0.58 – 1.0)[£]	1.1 (0.86 – 1.3)	1.0 (0.80 – 1.3)	0.61 (0.42 – 0.88)[$]	0.58 (0.39 – 0.86)[$]
Leukemia	0.64 (0.076 – 5.3)	0.47 (0.050 – 4.4)	0.85 (0.24 – 3.0)	0.77 (0.21 – 2.9)	0.63 (0.073 – 5.4)	0.82 (0.093 – 7.3)
Lymphoma	1.3 (0.26 – 6.3)	1.9 (0.34 – 11)	0.52 (0.16 – 1.8)	0.57 (0.17 – 2.0)	1.0 (0.21 – 5.2)	0.88 (0.16 – 4.8)
Hypertension	1.5 (1.2 – 1.8)[*]	1.0 (0.85 – 1.3)	1.5 (1.3 – 1.8)[*]	1.1 (0.94 – 1.3)	1.3 (1.1 – 1.7)[$]	1.4 (1.0 – 1.8)[$]
Valve disease	3.0 (2.0 – 4.6)[*]	2.3 (1.5 – 3.7)[*]	2.8 (2.1 – 3.7)[*]	2.0 (1.5 – 2.7)[*]	3.3 (2.2 – 5.0)[*]	2.9 (1.9 – 4.6)[*]

[*], $P < 0.001$; [$], $P < 0.05$; [£], $P < 0.10$; [μ], adjusted for age, gender, diuretics intake, β blocker intake, calcium channel inhibitor intake, ACE inhibitor intake, ARB intake, arterial

OR: odds ratio; CI: confidence interval; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 4 Determinants of receiving anticoagulants in the 6 months after the diagnosis of atrial fibrillation (Logistic regression analysis, n = 1830)

	Bivariate OR (95% CI)	*P* value	Multivariable OR 95% CI	*P* value
Age (years)	0.98 (0.96 – 0.99)	<0.001	1.00 (0.98 – 1.01)	0.74
Men	1.3 (1.1 – 1.6)	0.002	1.5 (1.2 – 1.8)	0.001
Medication				
Digitalis	1.9 (1.4 – 2.5)	<0.001	2.0 (1.4 – 2.7)	<0.001
Antiarrhythmic drug	2.4 (1.9 – 3.0)	<0.001	2.0 (1.6 – 2.5)	<0.001
Antihypertensive medication				
Diuretic	2.5 (2.1 – 3.0)	<0.001	1.5 (1.2 – 1.9)	0.001
β blocker	3.1 (2.5 – 3.7)	<0.001	2.4 (1.9 – 2.9)	<0.001
Calcium channel blocker	2.2 (1.7 – 2.8)	<0.001	1.6 (1.2 – 2.1)	0.003
ACE-inhibitor	2.1 (1.7 – 2.6)	<0.001	1.5 (1.1 – 1.9)	0.003
ARB	3.0 (2.2 – 4.3)	<0.001	2.3 (1.6 – 3.4)	<0.001
Comorbidity				
$CHADS_2$ score*	1.0 (0.94 – 1.1)	0.64	1.1 (0.99 – 1.3)$	0.079
CHA_2DS_2-VASc score*	0.98 (0.92 – 1.0)	0.57	1.1 (0.99 – 1.3)£	0.086
Charlson Comorbidity Index*	0.91 (0.86 – 0.96)	<0.001	0.90 (0.83 – 0.97)$	0.009
Myocardial infarction	1.0 (0.79 – 1.4)	0.77	0.84 (0.61 – 1.2)	0.29
Heart failure	0.99 (0.74 – 1.3)	0.92	1.0 (0.72 – 1.4)	0.92
Peripheral vascular disease	1.2 (0.86 – 1.7)	0.30	1.2 (0.80 – 1.7)	0.41
Stroke	1.1 (0.82 – 1.4)	0.66	1.2 (0.86 – 1.6)	0.32
Dementia	0.19 (0.097 – 0.38)	<0.001	0.26 (0.12 – 0.56)	<0.001
Chronic pulmonary disease	1.9 (1.0 – 3.4)	0.041	1.9 (0.97 – 3.7)	0.062
History of peptic ulcer	0.74 (0.53 – 1.0)	0.078	0.66 (0.45 – 0.96)	0.031
Liver disease	0.94 (0.55 – 1.6)	0.81	0.94 (0.51 – 1.7)	0.85
Diabetes	1.2 (0.96 – 1.6)	0.11	1.1 (0.85 – 1.5)	0.40
Hemiplegia	0.60 (0.28 – 1.3)	0.18	0.77 (0.33 – 1.8)	0.56
Renal disease	0.84 (0.73 – 0.97)	0.021	0.88 (0.74 – 1.0)	0.14
History of tumor	0.70 (0.53 – 0.93)	0.013	0.67 (0.49 – 0.92)	0.012
Leukemia	0.26 (0.029 – 2.3)	0.23	0.36 (0.038 – 3.5)	0.38
Lymphoma	1.4 (0.31 – 6.2)	0.66	0.93 (0.19 – 4.5)	0.92
Hypertension	1.3 (1.0 – 1.5)	0.016	1.0 (0.82 – 1.3)	0.86
Valve disease	1.2 (0.88 – 1.6)	0.24	1.2 (0.87 – 1.8)	0.24
Stroke in the first 6 months after diagnosis of atrial fibrillation	1.6 (1.0 – 2.6)	0.042	1.8 (1.0 – 3.1)	0.039

*, per point increase; $, adjusted for age, gender, digitalis intake, antiarrhythmic drug intake, diuretic intake, β blocker intake, calcium channel blocker intake, ACE inhibitor intake, ARB intake, valve disease, stroke in the first 6 months after diagnosis of atrial fibrillation and $CHADS_2$ or Charlson Comorbidity index; £, adjusted for age, digitalis intake, antiarrhythmic drug intake, diuretic intake, β blocker intake, calcium channel blocker intake, ACE inhibitor intake, ARB intake, valve disease, stroke in the first 6 months after diagnosis of atrial fibrillation and Charlson Comorbidity index.

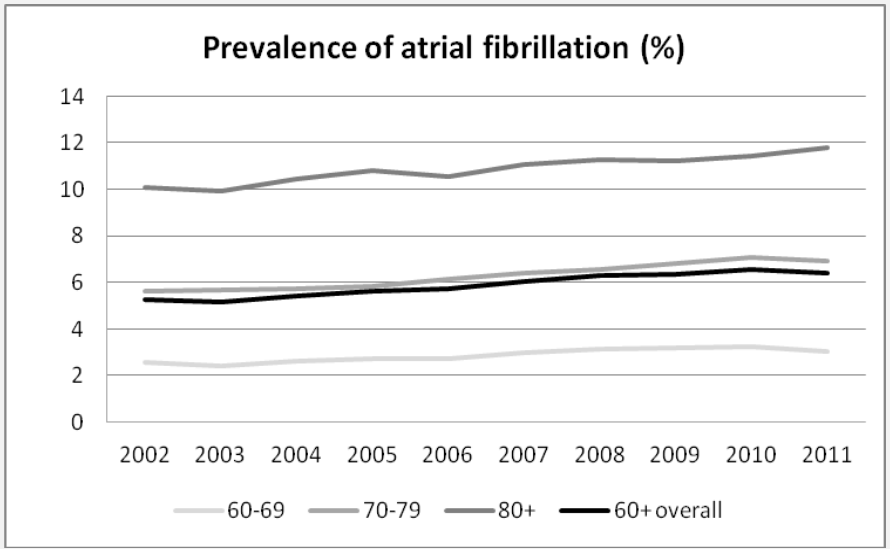
OR: odds ratio; CI: confidence interval; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 5 Predictors of stroke after the diagnosis of atrial fibrillation (Cox regression analysis, n = 1830)

	Bivariate HR (95% CI)	***P* value**	**Multivariable** HR 95% CI	***P* value**
Age (years)	1.06 (1.03 – 1.08)	<0.001	1.05 (1.03 – 1.07)	<0.001
Men	0.82 (0.61 – 1.1)	0.19	1.1 (0.76 – 1.5)	0.74
Comorbidity				
$CHADS_2$ score[*]	1.7 (1.5 – 1.9)	<0.001	1.5 (1.3 – 1.7)[$]	<0.001
CHA_2DS_2-VASc score[*]	1.5 (1.3 – 1.6)	<0.001	1.4 (1.2 – 1.6)[£]	<0.001
Charlson Comorbidity Index[*]	1.3 (1.2 – 1.4)	<0.001	1.1 (0.97 – 1.2)[$]	0.14
Myocardial infarction	0.87 (0.54 – 1.4)	0.55	0.64 (0.39 – 1.0)	0.075
Heart failure	1.2 (0.75 – 1.8)	0.48	0.90 (0.57 – 1.4)	0.65
Peripheral vascular disease	1.9 (1.2 – 2.9)	0.006	1.5 (0.94 – 2.3)	0.093
Stroke	5.6 (4.1 – 7.5)	<0.001	5.2 (3.8 – 7.2)	<0.001
Dementia	1.9 (0.93 – 3.8)	0.081	1.0 (0.48 – 2.1)	0.99
Chronic pulmonary disease	0.24 (0.034 – 1.7)	0.16	0.17 (0.024 – 1.2)	0.081
History of peptic ulcer	0.83 (0.46 – 1.5)	0.53	0.74 (0.41 – 1.3)	0.32
Liver disease	1.6 (0.82 – 3.1)	0.17	1.4 (0.69 – 2.8)	0.36
Diabetes	1.2 (0.80 – 1.7)	0.44	1.3 (0.87 – 1.9)	0.21
Hemiplegia	1.6 (0.61 – 4.4)	0.32	0.63 (0.23 – 1.8)	0.38
Renal disease	1.4 (1.2 – 1.7)	<0.001	1.3 (1.1 – 1.6)	0.006
History of tumor	1.3 (0.90 – 2.0)	0.15	1.1 (0.74 – 1.7)	0.59
Leukemia	3.3 (0.46 – 24)	0.23	3.1 (0.42 – 23)	0.27
Lymphoma	0.049 (0.0 – 2923)	0.59	0.0 (0.0 – $5.0 \times e^{161}$)	0.96
Hypertension	0.98 (0.73 – 1.3)	0.92	0.94 (0.69 – 1.3)	0.69
Valve disease	0.89 (0.53 – 1.5)	0.65	0.81 (0.48 – 1.4)	0.44

[*], per point increase; [$], adjusted for age, gender, valve disease and $CHADS_2$ or Charlson Comorbidity index; [£], adjusted for age, valve disease and
HR: hazard ratio; CI: confidence interval; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Figure 1 Prevalence and incidence of atrial fibrillation in the Intego database patients of 60 years and older.



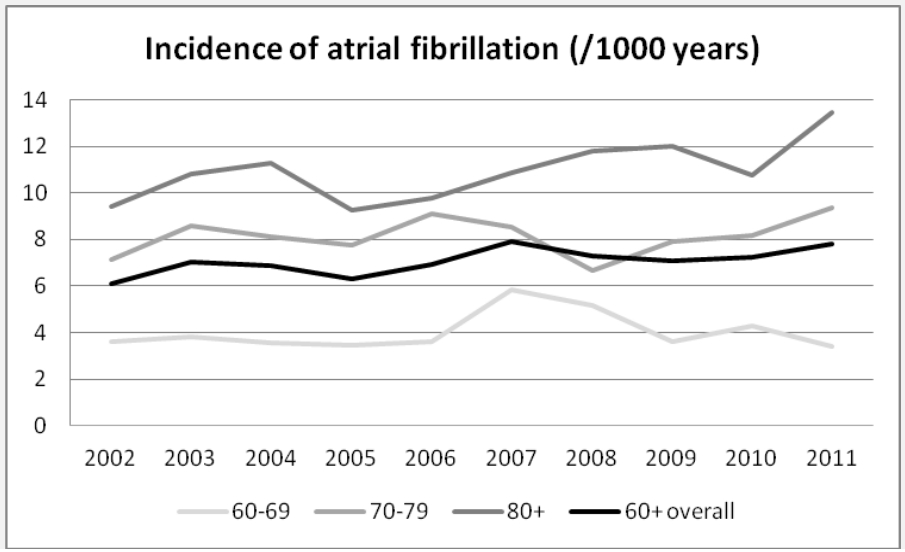


Figure 2 Anticoagulation treatment at time of stroke in AF patients (n=178)

