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Treatment patterns for oral anticoagulants in older patients with atrial fibrillation: a retrospective, cross-sectional, nationwide study from Denmark

Peter Vibe Rasmussen [ORCID],[1] Tharsika Sakthivel,[1] Frederik Dalgaard [ORCID],[1] Gunnar Hilmar Gislason,[1,2,3] Jannik Langtved Pallisgaard,[1] Morten Lock Hansen[1]

[1]Department of Cardiology, Herlev-Gentofte Hospital, Copenhagen, Denmark
[2]The Danish Heart Foundation, Copenhagen, Denmark
[3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Peter Vibe Rasmussen;
peter.vibe.rasmussen@gmail.com

ABSTRACT

Objectives Atrial fibrillation (AF) is a predominant risk factor of ischaemic stroke and treatment with oral anticoagulants (OACs) is recommended in all patients with risk factors. This study sought to examine treatment patterns of OACs in older patients with AF.

Design Retrospective, cross-sectional study.

Setting Danish nationwide administrative and clinical registers and databases.

Participants A total of 40 027 patients, ≥75 years of age, after their first hospital contact due to AF between 2010 and 2018.

Primary and secondary outcomes measures The primary event of interest was claimed prescriptions for OACs within 180 days after first hospital contact due to AF. Proportions of patients treated with OACs were estimated and clinical factors associated with the probability of receiving OAC treatment were identified using adjusted logistic regression models.

Results A total of 40 027 patients were included with a slight majority of women (54%). The median age was 81 years (IQR 78–86). We found that an overall 32 235 patients (81%) were prescribed an OAC after their first hospital contact due to AF with a marked increase in the proportion of patients treated from 2010 to 2018. Factors related to a decreased probability of receiving treatment were bleeding risk factors such as a history of haemorrhagic stroke (OR 0.21, 95% CI 0.16 to 0.27), any bleeding (OR 0.58, 95% CI 0.53 to 0.62) as well as markers of frailty such as osteoporosis (OR 0.78, 95% CI 0.71 to 0.85).

Conclusion In this large nationwide study, we found that in older patients with AF, the overall rates of OAC prescription were generally high (~80%) and increasing during the last decade. Factors associated with not receiving guideline recommended OAC treatment were generally related to bleeding risk factors or frailty.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence that increases notably with age.[1] AF

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This nationwide study investigated treatment with oral anticoagulants (OACs) in older patients (≥75 years) with atrial fibrillation and was able to demonstrate high rates of treatment with OACs, which have increased over time.

⇒ This study used a large contemporary study population without missing data or lost to follow-up.

⇒ Diagnostic coding was based on the International Classification of Diseases 10th Revision, which is known to be susceptible to misclassification bias, and certain clinical information such as biochemical data were not available.

frequently presents itself with potentially debilitating symptoms such as palpitations, dyspnoea and chest discomfort.[2] However, the main concern from a clinical perspective is related to the fact that AF is associated with an at least fivefold increased risk of thromboembolic events, most notably, ischaemic stroke.[3] Hence, initiation of prophylactic treatment with oral anticoagulants (OACs) is recommended in all patients with thromboembolic risk factors.[4] OAC treatment has traditionally been comprised by the vitamin-K antagonists (VKAs), however, in recent years, the direct OACs (DOACs) have become the first-line treatment of choice demonstrating at least non-inferior safety and efficacy compared with VKAs also in older patients.[5]

Importantly, the reduction in the risk of ischaemic stroke with OAC treatment comes with an increased risk of bleeding.[6 7] While increasing age increases the risk of stroke, stressing the importance of OAC treatment in older patients, increasing age is also associated with increased prevalence of multimorbidity, polypharmacy, frail vessels as well as an increased tendency to fall, which are

all predisposing factors of bleeding.[8] Hence, initiation of OAC treatment in older frail patients often call for complex risk–benefit considerations by the treating physician. As such, several studies have raised the important question as to whether OAC treatment is generally underutilised in older patients in real-world practice.[9 10]

Using Danish nationwide administrative registers and clinical databases, we sought to describe a nationwide population of older patients with AF (≥75 years of age) and their associated treatment with OACs.

METHODS

We did a retrospective, cross-sectional study using Danish nationwide administrative and clinical registers and databases. The reporting of data was done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11]

Registers and databases

Citizens with permanent residence in Denmark are assigned a unique civil registration number enabling linkage of several administrative healthcare registers on an individual level.[12] Using these different registers, it is possible to follow individuals regarding hospital diagnoses, performed procedures and operations, filled drug prescriptions and mortality. The Danish National Patient Register contains information regarding hospital admissions, consultations at outpatient clinics as well as data on performed procedure or operations.[13] All diagnostic codes used in this study are classified according to the International Classification of Diseases 10th edition. Every hospital contact is registered with a primary diagnostic code and one or more secondary diagnoses codes if deemed appropriate.

The Danish National Prescription Registry contains information on claimed prescriptions in Denmark with the therapeutic agent classified according to the ATC system (Anatomical Therapeutic Chemical Classification).[14] Information regarding dispensing date, quantity of tablets per package, drug strength, number of packages and drug type can be obtained from this registry.

The data in the leveraged registers have been used extensively for research during the preceding decades and are continuously undergoing scrutiny of data quality and manual validation.[15]

Study population

We included all Danish patients >75 years of age with a primary diagnosis of AF or atrial flutter (Both referred to as AF in the following). Patients were included at their first hospital contact due to AF between 2010 and 2018 and only patients surviving 180 days from their index hospitalisation were included. The study was restricted to a period in which guidelines have consistently advised for OAC treatment using the CHA_2DS_2-VASc score (after October 2010). Inherent to our study design, only patients with a CHA_2DS_2-VASc score of >2 were included. Patients

were excluded if they were not residing in Denmark or if they migrated from the country directly after hospital discharge.

Factors and variables of interest

The primary outcome of the study was defined as treatment with any OAC (warfarin, phenprocoumon, rivaroxaban, apixaban, dabigatran or edoxaban) after the first hospital contact due to AF. We identified prescriptions claimed at any pharmacy in a period of 180 days following discharge for the first hospital contact due to AF. Regarding treatment with a DOAC, we only included dosages recommended and approved by the Danish Health and Medicines Authority for thromboprophylaxis in AF (apixaban 5 mg two times per day, dabigatran 150 mg two times per day, rivaroxaban 20 mg once daily and edoxaban 60 mg once daily). Some patients were treated with reduced dosage as this is recommended when specific criteria are met. Reduced dose was defined according to the reduced doses recommended and approved by the Danish Health and Medicines Authority (apixaban 2.5 mg two times per day, dabigatran 110 mg two times per day, rivaroxaban 15 mg once daily and edoxaban 30 mg once daily).

A range of factors hypothesised as influential in the clinical decision-making regarding treatment with OACs in older patients was included in the study. These factors included certain demographic variables, comorbidities as well as concomitant pharmacotherapies further specified in the following.

Comorbidities and concomitant pharmacotherapy

Comorbidities were defined as a registered diagnosis during hospital admissions or visits to outpatient clinics in a period of 5 years prior to or on the date of the index hospital contact. Concomitant treatment with pharmacotherapy was defined as any filled prescription at any pharmacy in Denmark 180 days prior to or on the date of interest. Comorbidities of interest included in the study were diabetes mellitus, ischaemic stroke/transient ischaemic attack (TIA)/Systemic embolism, any history of thromboembolic disease, bleeding, haemorrhagic stroke, hypertension, venous thromboembolism, chronic obstructive pulmonary disease, heart failure (HF), ischaemic heart disease (IHD), vascular disease, cancer, diagnoses of liver disease, diagnoses associated with alcohol abuse, diagnoses of kidney disease, peptic ulcer, osteoporosis, arthritis, a tendency to fall (defined as a history of consultations at a specialised clinic or a diagnosis of falling), dementia, traumatic injury, a range of diseases of the central nervous system, thyroid disease, depression, anaemia, valvular heart disease, any prior percutaneous coronary interventions, coronary artery bypass grafting, and pacemaker or implantable cardioverter defibrillators.

Concomitant pharmacotherapy of interest was defined as treatment with non-loop- or loop diuretics, proton-pump inhibitors, beta-blockers, calcium-antagonists, renin–angiotensin system inhibitors,

digoxin, acetylsalicylic acid (ASA), dipyridamole agents, adenosine-diphosphate inhibitors, lipid-lowering drugs, non-steroidal anti-inflammatory drugs (excluding glucosamines) and glucocorticoids. Polypharmacy was defined as the treatment with >4 of the included drugs at the same time. Dual antiplatelet treatment (DAPT) was defined in this study as claimed prescriptions for both ASA and adenosine-diphosphate inhibitors.

Diabetes mellitus and thyroid disease were defined using ATC-codes for pharmacotherapy used to treat these disorders. Alcohol abuse, dementia and depression were defined as either a diagnosis or claimed prescriptions for medication used to treat the condition. Hypertension was defined as the treatment with more than one class of antihypertensive drug at the same time as previously done.[16] Patient CHA_2DS_2-VASc scores were calculated in accordance with the most recent recommendations by the European Society of Cardiology.[4] For details on variable definitions, please see online supplemental tables 1 and 2.

Statistical methods

The study population was described at baseline using descriptive statistics with continuous variables reported as medians with corresponding IQRs and categorical variables with counts and percentages. The proportion of patients treated with OACs after being diagnosed with AF were depicted graphically. Moreover, the temporal trends in the proportion of patients being treated with OACs during the study period were investigated and depicted graphically.

The association between the included clinical factors, hypothesised as influential regarding OAC treatment decisions, and the odds of OAC treatment were estimated using a series of adjusted logistic regression models and presented using forest plot. Estimates were presented as adjusted OR with 95% CI. In addition to the factors of interest, the models were adjusted for age, sex, calendar year, as well as previous bleeding (when appropriate).

All statistical analysis was performed in R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Patient and public involvement

None.

RESULTS

A total of 40 027 patients with AF were included in the study with a slight predominance of women (54%). The median age was 81 years (IQR 78–86) having a median CHA_2DS_2-VASc score of 4 (IQR 3–4) (table 1 and online supplemental table 3).

Among the most common comorbidities found in the study population were a history of hypertension (59%), IHD (19%), cancer (14%), HF (15%), depression (14%) and ischaemic stroke (12%) (table 2).

Table 1 Baseline characteristics (N=40 027)

Male sex (%)	18 442 (46)
Age (median (IQR))	81.00 (78.00–86.00)
CHA_2DS_2-VASc (median (IQR))	4.00 (3.00–4.00)
Non-loop diuretics (%)	15 120 (38)
Loop diuretics (%)	10 749 (27)
Proton-pump inhibitors (%)	10 522 (26)
Beta-blocker (%)	17 238 (43)
Calcium-antagonist (%)	12 042 (30)
RAS-inhibitor (%)	18 728 (47)
Digoxin (%)	4025 (10)
ASA (%)	14 174 (35)
Dipyridamole agent (%)	1060 (3)
ADP-inhibitor (%)	4199 (11)
Lipid-lowering drugs (%)	15 535 (39)
NSAID (%)	5118 (13)
Glucocorticoids (%)	3996 (10)
Methotrexate (%)	418 (1)
Polypharmacy (%)	14 328 (36)
Any antiplatelet therapy (%)	17 013 (43)
DAPT (%)	1479 (4)

ADP-inhibitor, adenosine diphosphate inhibitor; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; NSAID, non-steroid anti-inflammatory drugs; RAS-inhibitor, renin–angiotensin system inhibitor.

Notably, treatment with antiplatelet drugs was very common at index hospitalisation for AF. As such, 35% were in treatment with ASA, 11% with an ADP-inhibitor and 4% had claimed prescriptions for DAPT.

Of the included patients, 32 235 (81%) claimed at least one prescription for any OAC treatment after the first hospital contact due to AF in the study period. Out of these patients, 19 239 (60%) were prescribed a DOAC and 9329 (49%) of those prescribed a DOAC received treatment in a reduced dosage. Dose reduction among the different DOACs was most common in patients treated with dabigatran (76%), and to a lesser extent apixaban (47%), rivaroxaban (31%) and edoxaban (31%).

Increasing age was associated with a clear tendency towards a decreased probability of receiving OAC treatment. As such, among patients aged 75 years, 85% received OAC treatment decreasing to 68% in patients aged 90 years (figure 1).

Collectively during the study period, a substantial increase in the proportion of patients treated with OACs was observed. As such, in 2011 63% claimed OAC prescriptions whereas this proportion increased to 92% in 2018 (figure 2).

Factors associated with OAC treatment

Generally, comorbidities and concomitant pharmacotherapy associated with an increased bleeding risk, risk

Table 2 Comorbidites (N=40 027)

Diabetes mellitus (%)	4769 (12)
Thromboembolism	5457 (14)
Ischaemic stroke/TIA/SE (%)	4650 (12)
Pulmonary embolism (%)	908 (2)
Bleeding	4003 (10)
Haemorrhagic stroke (%)	262 (1)
Hypertension (%)	23 438 (59)
VTE (%)	1645 (4)
COPD (%)	4328 (11)
Heart failure (%)	5912 (15)
IHD (%)	7692 (19)
Vascular disease (%)	7207 (18)
Cancer (%)	5646 (14)
Liver disease (%)	316 (1)
Alcohol abuse (%)	484 (1)
Kidney disease (%)	2270 (6)
Peptic ulcer (%)	1073 (3)
Osteoporosis (%)	3472 (9)
Arthritis (%)	1794 (5)
Tendency to fall (%)	2723 (7)
Dementia (%)	1359 (3)
Traumatic injury (%)	5554 (14)
CNS disease (%)	1733 (4)
Thyroid disease (%)	3128 (8)
Depression (%)	5586 (14)
Anaemia (%)	2982 (7)
Valvular heart disease (%)	4517 (11)
PCI (%)	3420 (9)
CABG (%)	2060 (5)
Pacemaker or ICD (%)	2996 (8)

CABG, coronary artery bypass grafting; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

Figure 1 Patient streated with oral anticoagulants (OAC), by age plot depicting the proportion of patients treated with OACs by age (blue curve). The red bar charts depict the number of patients in each age category. The x-axis illustrates age in years and the left y-axis shows the proportion of patients treated with OACs in percentage (%). The right y-axis depicts the absolute number of patients.

95% CI 0.33 to 0.42), osteoporosis (OR 0.78, 95% CI 0.71 to 0.85), depression (OR 0.71, 95% CI 0.67 to 0.76) and a tendency to fall (OR 0.56, 95% CI 0.51 to 0.62).

of falling or general frailty conferred decreased odds of receiving OACs. As such, having a history of any bleeding conferred a decreased probability of OAC treatment (OR 0.58, 95% CI 0.53 to 0.62), which was accentuated when examining haemorrhagic stroke (OR 0.21, 95% CI 0.16 to 0.27). Treatment with antiplatelet drugs were associated with reduced odds of OAC treatment (OR 0.74, 95% CI 0.70 to 0.78) especially among patients in treatment with DAPT (OR 0.52, 95% CI 0.47 to 0.59). Moreover, bleeding risk factors such as kidney disease, liver disease and alcohol abuse also conferred decreased odds of OAC treatment (figure 3).

Frailty markers were strongly associated with decreased odds of OAC treatment such as dementia (OR 0.37,
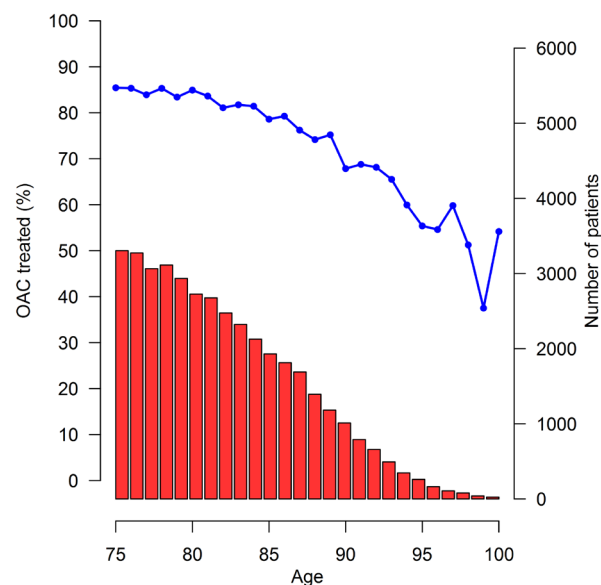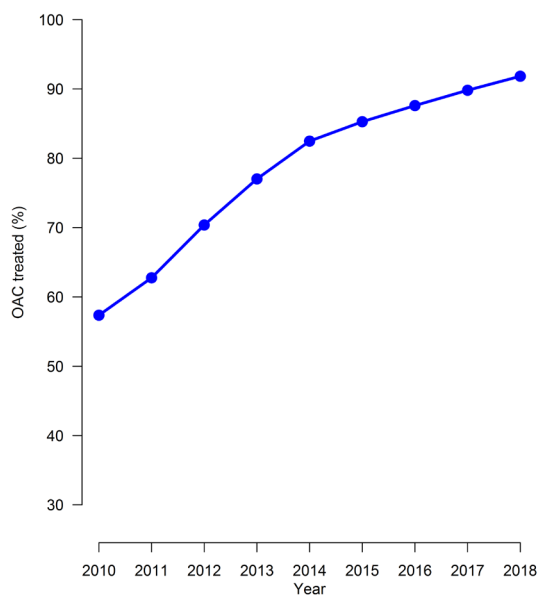

Figure 2 Proportion of patients receiving treatment with oral anticoagulants (OACs) by calendar year the x-axis illustrates year and the y-axis the proportion in percentage (%).
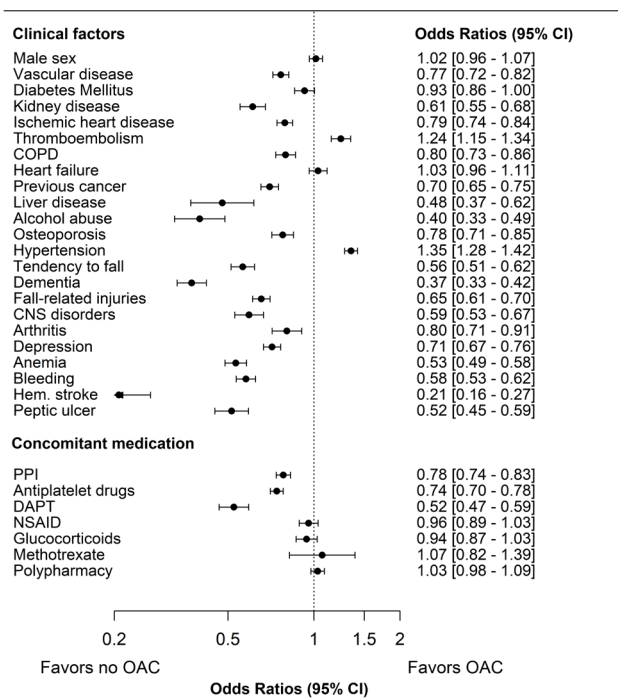
Figure 3 Forest plot depicting the association between clinical factors and the odds of receiving treatment oral anticoagulants (OAC) the x-axis illustrates ORs with 95% CI and the investigated factors are depicted on the y-axis. CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

Oppositely, several conventional stroke risk factors were associated with an increased probability of OAC treatment such as previous thromboembolism (OR 1.24, 95% CI 1.15 to 1.34) and hypertension (OR 1.35, 95% CI 1.28 to 1.42) (figure 3).

DISCUSSION

In this large nationwide study of older patients (≥75 years of age) with AF, we uncovered several interesting findings. During the last decade, approximately 8 out of 10 of all older patients with AF were treated with OACs in Denmark. This proportion increased substantially during the period surpassing 90% around 2017. While the overall prescription rate of OACs was high, several factors were associated with a decreased probability of receiving guideline-directed treatment with OACs. These factors were generally related to bleeding risk factors and markers of frailty.

AF confers a markedly increased risk of thromboembolic events, most notably ischaemic stroke, and the effectiveness of OACs in reducing the risk of stroke has been known for decades.[17] While reducing the risk of ischaemic stroke, OAC treatment concurrently increases the risk of bleeding.[6] In older patients, the risk of stroke as well as the OAC associated risk of bleeding are both increased. However, as the risk of stroke increases more steeply

with age than the risk of bleeding, the absolute benefit of OACs has been reported to be the highest in older patients.[18–20] Consequently, OACs are more or less universally recommended in patients with AF and stroke risk factors irrespective of advanced age or multimorbidity.[4] In addition, DOACs have been shown to be at least non-inferior in older patients compared with VKAs.[21] Nevertheless, from the perspective of the treating clinician, the decision to anticoagulate is often comprised by complex risk-benefit considerations weighing the harm of potential bleeding against the benefit of stroke risk reduction. In this view, our findings of a relatively high proportion of patients receiving guideline-directed treatment (~80%), especially during the more contemporary years, are reassuring. However, among the very old patients, the proportion of patients treated with OACs remains lower.

Several real-world studies have previously suggested a notable underusage of OACs in clinical practice among older patients but, reassuringly, more contemporary investigations are in line with our data reporting OAC prescription rates above 80%.[9 10 22]

Foregoing treatment with OACs in clinical practice possibly relates to a range of factors pertaining to both the patient as well as the treating physician.[23] As such, our data suggest that factors relating to the risk of bleeding such as previous haemorrhagic stroke or peptic ulcer as well as general markers of frailty are of potential importance when deciding not to anticoagulate in clinical practice. It is also noteworthy, that treatment with antiplatelet drugs, especially DAPT, decreases the likelihood of OAC treatment. This is likely also the key driver behind the observed decreased odds of OAC treatment associated with IHD and vascular disease.

Interestingly, previous fall-related injuries, as well as having a history of consultations at specialised clinics for patients with a history of falling, seem to confer markedly decreased probabilities of OAC treatment. These data are interesting since being prone to falling should not necessarily in itself exclude older patients from receiving guideline-directed therapy with OACs and the evidence regarding the risk–benefit ratio in these patients are still poorly understood.[4 24 25]

In line with these findings, studies from both Scandinavia and the USA have ascertained that increasing morbidity burden, often a key marker of frailty, is associated with decreasing likelihood of OAC treatment in older patients with AF.[26 27] Collectively, these data underline a potential clinical dilemma as patients with risk factors and multimorbidity are potentially the patients who benefit the most from the treatment.

Published Danish data have also shown that socioeconomic status is of importance regarding the probability of receiving OAC treatment, although the specific mechanisms are unknown.[28]

Left atrial appendage occlusion was during the study period in Denmark a procedure used in a very small, selected group of older patients with AF and is likely not a contributing explanation to the study results.

It should be noted that even though the majority of available studies support the notion of a nearly universal benefit of OACs across all patient subgroups, recent data have challenged this perception suggesting that the net clinical benefit of OACs in the oldest patients could potentially be lower than previously assumed.[29]

Conclusively, our data suggest that the overall adherence with guideline-directed initiation of OAC treatment in older patients with AF in Denmark is high. However, specific subgroups such as patients with bleeding risk factors and multiple comorbidities warrant further studies and attention.

Limitations

The major limitations of this study are related to the observational study design and the data from the leveraged registers. As such, even though many of the important diagnoses used in this study have been validated, some have not.[15 30] Reassuringly, key variables such as our used definition of AF as well as prescriptions of OAC treatment have been manually validated with high positive predictive values and data completeness.[31 32]

Importantly, the used registers do not contain any information on the reason for not initiating treatment with OACs. As such, the reasons for foregoing treatment could be fully justified. Hence, we did not have information on potential contraindications such as allergies, estimated glomerular filtration rates, or data relating to patient preferences (eg, not agreeing to the treatment). Regarding depression, diagnoses exclusively registered at psychiatric hospitals were not included in the study. However, this was accounted for using medication used in the treatment of depression for defining the condition. Moreover, the employed definitions of diabetes, hypertension and thyroid disease used claimed prescriptions for medications used for treating these conditions. As such, patients managed with non-pharmacological interventions as well as non-adherent patients could lead to some degree of underestimation.

Moreover, patients treated with hospital administered low-molecular weight heparins will not be captured in our study. Finally, patients treated exclusively in primary care and never receiving a primary hospital diagnosis of AF will not be included in our study. This is likely to represent a degree of selection bias in the study population, which should be acknowledged when interpreting the findings of the study.

CONCLUSIONS

In this nationwide observational study of older AF patients ($\geq$75 years of age), we found that the overall prescription rates of OAC treatment were high (~80%) with a clear trend towards higher rates in the most contemporary years of the study. Factors associated with decreased likelihood of OAC treatment were generally related to bleeding risk factors or markers of frailty and multimorbidity.

ORCID iDs
Peter Vibe Rasmussen http://orcid.org/0000-0002-4593-3854
Frederik Dalgaard http://orcid.org/0000-0002-7287-4191

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