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ORIGINAL PAPER

Uptake in antithrombotic treatment and its association with stroke incidence in atrial fibrillation: insights from a large German claims database

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Abstract

Background Underuse of oral anticoagulation (OAC) for stroke prevention in atrial fibrillation (AF) results in thousands of preventable strokes in Germany each year. This study aimed to assess changes in antithrombotic therapy in AF patients after increased use of direct oral anticoagulants (DOACs) in Germany and to evaluate whether the adoption of DOAC therapy was associated with changes in AF-related stroke and bleeding over time.

Methods Analyses were carried out on a large claims-based dataset of 4 million health-insured Germans. The study population consisted of 601,261 prevalent AF patients between 2011 and 2016 who were assigned to one of the following four treatment groups: DOAC, VKA, antiplatelets or no antithrombotic treatment. Treatment patterns were descriptively analysed and represented by cohort and CHA_2DS_2-VASc score. Clinical outcomes before and after the adoption of DOAC therapy were assessed using Poisson regression models.

Results Use of OAC increased from 42 to 61% between 2011 and 2016, mainly due to more frequent prescription of DOACs. However, some underuse of OAC therapy remained even in high risk AF patients. In parallel with the increased prescription rate of OAC, there was an overall 24% incidence reduction in stroke between 2011 and 2016 which was mainly driven by reductions in ischemic strokes. Over the same time period the risk for major bleeding remained unchanged.

Conclusion Between 2011 and 2016, the use of guideline-conform antithrombotic therapy in Germany has significantly increased. This was associated with a significant decline in strokes without an increased incidence of bleeding complications.

Keywords Atrial fibrillation · Oral anticoagulation · Direct oral anticoagulants · VKA · Stroke

Introduction

Vitamin K antagonists (VKA) have been the mainstay of antithrombotic therapy for stroke prevention in atrial fibrillation (AF) over several decades. However, they proved to be difficult to use, which, together with safety concerns, limited their wide-spread use [1]. As a result, a significant number of AF patients did not receive guideline-recommended oral anticoagulation (OAC) therapy, particularly elderly and frail patients [1, 2]. Since 2009, four direct oral anticoagulants (DOAC) have been approved for stroke prevention in AF which have been demonstrated to be at least as effective and in general significantly safer than VKA. Several studies and registries have shown that DOACs are being increasingly used for stroke prevention in AF and that accordingly more patients are receiving guideline-endorsed OAC therapy [3–8]. It is currently not known if these changes also apply for AF patients treated in Germany; moreover, it remains to be determined whether the increased use of DOACs has resulted in improved clinical outcomes. The present retrospective observational study therefore had two major objectives: First, to assess changes in antithrombotic therapy in AF patients after the more wide-spread use of DOACs in

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Germany between 2011 and 2016; and second, to evaluate whether the adoption of DOAC therapy has resulted in changes in AF-related outcomes over time.

Methods

Study design and data source

This retrospective observational study was conducted using an anonymized claims-based dataset from the Institute for Applied Health Research (formerly Health Risk Institute, Berlin). The database contains longitudinal information on medical and drug claims from an age- and gender-representative sample of about 4 million statutory health-insured subjects in Germany, representing approximately 5% of the total population. External validity of this database against German population data has been shown previously [9]. In brief, the database includes demographic information, ambulatory services and diagnoses, hospital data including diagnoses and procedures, reimbursed remedies and aids as well as dispensations of reimbursed drugs. All diagnoses in the database were coded according to the German modification of the 10th revision of the International Classification of Diseases (ICD-10 GM). Pharmacy claims include various information on all outpatient prescriptions dispensed in German pharmacies like dispensing/prescription date, and number of tablets dispensed. Prescription handouts were coded according to the Anatomical Therapeutic Chemical Classification System (ATC).

Patient-level data can be arrayed chronologically to provide a detailed longitudinal profile of all medical and pharmacy services used by each insured member. All patient identifiers were either fully encrypted or removed from the database which is, therefore, compliant with the German data protection regulations. As no patient contact was made and patient information was de-identified, Institutional Review Board approval was not required.

Study population

The study population consisted of all prevalent patients with an inpatient or secured outpatient diagnosis of AF between January 1, 2011, and December 31, 2016. The index date was defined as the date of inpatient or outpatient AF diagnosis and the index quarter as a quarter in which the AF diagnosis was documented. To focus on stroke prevention in AF several inclusion and exclusion criteria were applied. Patients with pulmonary embolism or deep vein thrombosis, valvular AF, pregnancy or hemodialysis, with anticoagulation therapy for any other indication on index date as well as patients who were prescribed more than one OAC agent on the index date were excluded. In addition, patients were required to have continuous enrollment in the database for 4 quarters prior to the index quarter and 4 quarters after the index quarter or until death. Derivation of the study population is shown in Fig. 1.

Antithrombotic treatment among study patients and study outcomes

Based on their prescribed treatment, patients were assigned to one of the following 4 treatment groups: DOAC (apixaban, dabigatran, rivaroxaban, or edoxaban), VKA (98% phenprocoumon, 2% warfarin), antiplatelets only, or no antithrombotic treatment.

The first objective of the study was to assess the proportion of German AF patients who did receive guideline-recommended antithrombotic therapy. This was evaluated over the entire study period as well as for each of the 6 sequential annual cohorts separately (years 2011–2016). Patients prescribed both an OAC and antiplatelets were categorized as OAC users.

The second objective was to determine whether changes in OAC over time resulted in changes in clinical outcomes including all-cause strokes, ischemic strokes, hemorrhagic strokes, and major bleedings (including intracranial bleeds) (defined as hospital discharge diagnoses; Tables S1 and S2 in Supplement). To particularly analyze the impact of the introduction of DOACs in Germany on the incidence of clinical outcomes, these were evaluated before and after the introduction of DOACs, i.e., in AF patients identified in 2011 and 2016, respectively; all patients were followed through four subsequent quarters after the index quarter. To allow for comparisons by years, a sensitivity analysis was performed where the primary outcome events were assessed in the year following the index quarter, i.e., in 2012 and 2017.

Statistical analysis

Baseline characteristics of the study population were reported as percentages or means ± standard deviation (SD) and were examined during 4 quarters prior to index quarter.

Treatment patterns were descriptively analysed for each of the 6 annual cohorts and represented separately for the entire study period, by cohort and according to the baseline CHA_2DS_2-VASc score of the patients. Additionally, the association between patient characteristics and the use of antithrombotic therapy was examined using a multinomial logistic regression model. Adjusted odds ratios (ORs) were reported for each risk factor, together with their 95% confidence intervals (CIs).

Clinical outcomes before and after the adoption of DOAC therapy were assessed using Poisson regression models with

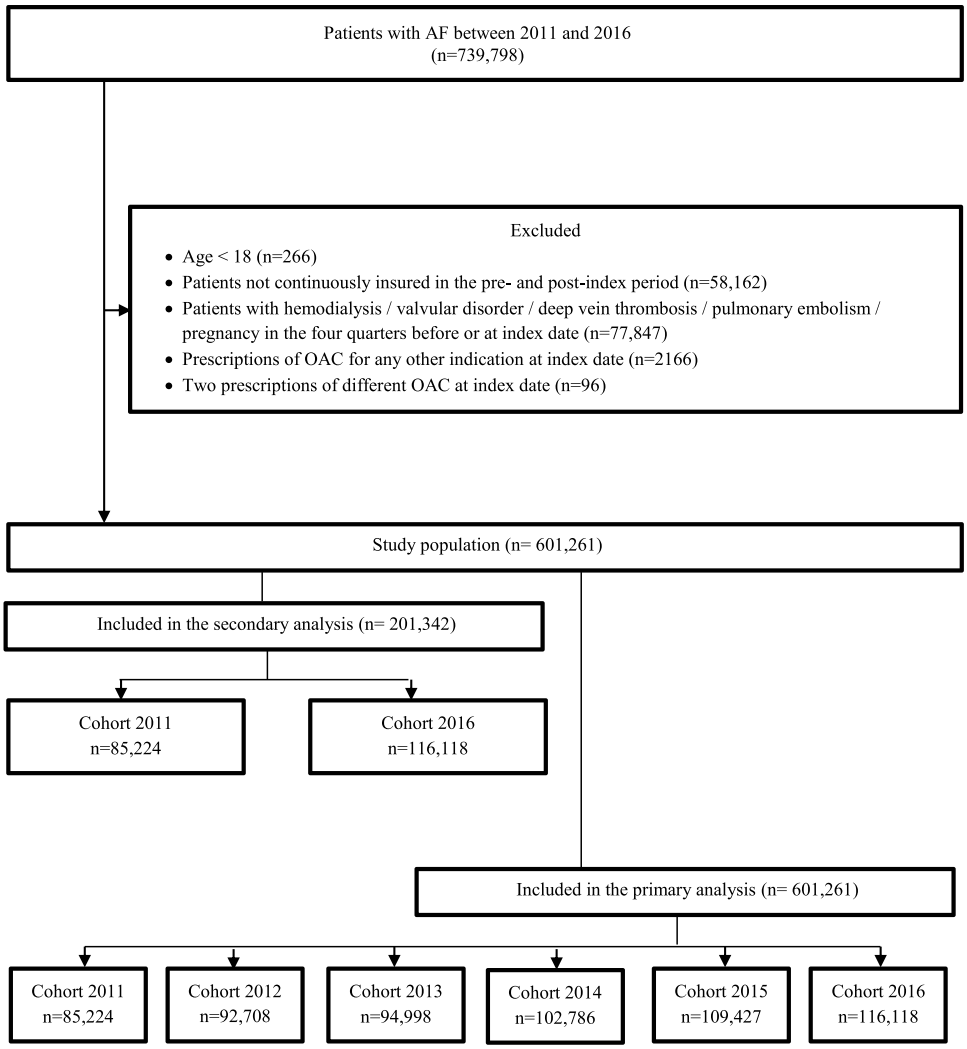

Fig. 1 Derivation of the analysis cohorts

a log link. Incidence rates (IRs) per 100 person-years were estimated for each of the outcome events in both cohorts of AF patients. Then incidence rate ratios (IRRs) were computed for comparisons of cohorts. IRs and IRRs were reported with 95% confidence intervals (CIs). To account for possible differences in patients characteristics in 2011 and 2016 cohorts, models were adjusted for age, gender, the components of CHA_2DS_2-VASc score; history of myocardial infarction; dementia/senility; kidney disease; history of major, gastrointestinal or intracranial bleeding; history of electrical cardioversion or catheter ablation; treatment with antiplatelets, beta blockers, and antiarrythmic drugs (amiodarone, dronedarone, propafenone, flecainide, and sotalol). To specifically assess the effect of change in anticoagulation treatment additional adjustment was made for OAC treatment. Prespecified subgroup analyses were performed for age and CHA_2DS_2-VASc scores.

Data analysis was carried out by the Institute for Applied Health Research, Berlin. Data management and statistical analyses were performed using SAS 9.3 (SAS Institute Inc.) and R 3.4.1. A two-sided p value < 0.05 was considered statistically significant.

Results

Patient population

The overall study population for addressing the first study objective comprised 601,261 prevalent AF patients enrolled in six sequential cohorts between 2011 and 2016. Overall, 63.2% of patients ($n = 379{,}950$) did receive an antithrombotic therapy while 36.8% ($n = 221{,}311$) did not (Table 1). Among 379,950 treated patients, 213,208 (56.1%) were treated with VKA, 102,574 (27.0%) treated with DOAC, and 64,168 (16.9%) were prescribed antiplatelets. Patients who did not receive any treatment were younger and had less comorbidities. Among treated patients, antiplatelet users were on average older and had more comorbidities compared with VKA and DOAC users.

Table 1 Baseline characteristics of the overall study population

Characteristic	No Therapy ($n=221,311$)	Therapy ($n=379,950$)	Antiplatelets ($n=64,168$)	VKA ($n=213,208$)	DOAC ($n=102,574$)
Patient demographics					
Age (mean ± SD)	73.8 (12.7)	75.6 (9.4)	77.7 (10.0)	75.2 (8.8)	75.0 (10.2)
Age groups (%)					
< 65 years	20.8	12.3	10.4	11.6	14.8
65–74 years	23.7	27.9	22.3	29.9	27.2
75–84 years	35.7	43.4	40.5	45.5	41.1
≥ 85 years	19.8	16.4	26.8	13.0	16.9
Male (%)	55.8	59.3	60.3	61.2	54.8
Index year (%)					
2011	17.0	12.5	18.2	16.5	0.6
2012	17.4	14.3	18.6	17.4	4.9
2013	16.2	15.6	16.5	17.0	12.0
2014	16.6	17.4	16.3	16.8	19.2
2015	16.4	19.2	15.6	16.6	27.0
2016	16.3	21.1	14.7	15.7	36.2
Medical history					
CHA_2DS_2-VASc (mean ± SD)	3.5 (1.8)	4.0 (1.6)	4.4 (1.6)	3.9 (1.5)	3.9 (1.7)
CHA_2DS_2-VASc, groups (%)					
CHA_2DS_2-VASc = 0	4.5	1.1	0.7	1.0	1.5
CHA_2DS_2-VASc = 1	10.5	4.9	3.5	4.8	6.0
CHA_2DS_2-VASc ≥ 2	85.0	94.0	95.8	94.2	92.5
Modified HAS-BLED score (mean ± SD)	2.4 (1.1)	2.7 (1.0)	3.3 (1.0)	2.5 (1.0)	2.6 (1.1)
Charlson comorbidity index (mean ± SD)	3.3 (3.0)	3.6 (2.9)	4.6 (3.1)	3.3 (2.7)	3.6 (2.9)
Comorbidities					
Hypertension (%)	82.8	90.0	91.8	89.5	89.9
Congestive heart failure (%)	33.5	39.2	46.6	37.7	37.6
Peripheral arterial disease (%)	10.2	12.6	20.0	11.1	10.9
Ischemic stroke (%)	4.7	8.0	10.2	5.9	10.8
Myocardial Infarction (%)	3.3	6.3	15.6	4.3	4.7
Diabetes mellitus (%)	31.5	39.3	43.6	39.9	35.5
Renal insufficiency (%)	20.1	21.2	29.3	19.1	20.5
Dementia/Senility (%)	16.3	15.3	24.4	11.3	18.2
Major bleeding (%)	5.2	4.1	7.9	2.7	4.6
Intracranial bleeding (%)	1.0	0.6	1.1	0.2	0.9
Gastrointestinal bleeding (%)	3.0	2.4	3.8	1.8	3.0
Ablation (%)	1.5	2.1	0.8	1.7	3.7
Cardioversion (%)	4.2	8.2	4.7	6.7	13.4
Concomitant medications					
Antiplatelets (%)	9.1	21.1	76.0	8.1	13.8
VKA (%)	30.8	54.8	19.0	86.2	11.9
DOAC (%)	4.5	19.0	4.4	1.4	64.7
Beta-blockers (%)	65.3	74.2	72.2	75.4	72.8
Amiodarone (%)	4.5	5.0	5.2	4.9	5.1
Dronedarone (%)	1.1	1.3	0.8	1.4	1.4
Flecainide (%)	3.7	2.9	1.6	2.8	3.9
Propafanone (%)	1.0	0.7	0.6	0.7	0.8
Sotalol (%)	1.3	1.1	1.0	1.3	0.8

CHA_2DS_2-VASc congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category, modified HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly (> 65), drugs/alcohol concomitantly

The study population to address the second study objective comprised 201,342 prevalent AF patients who were identified in the years 2011 ($n = 85{,}224$) and 2016 ($n = 116{,}118$), respectively. The distribution of demographic and clinical characteristics are depicted in Table 2.

Table 2 Baseline characteristics of the study population in cohorts 2011 and 2016

Characteristic	Cohort 2011 ($n = 85{,}224$)	Cohort 2016 ($n = 116{,}118$)
Age (mean ± SD)	74.3 (10.9)	75.4 (10.8)
Age groups (%)		
< 65 years	16.2	14.9
65–74 years	29.4	23.6
75–84 years	38.7	42.4
≥ 85 years	15.8	19.1
Male (%)	58.3	57.7
CHA_2DS_2-VASc (mean ± SD)	3.7 (1.7)	3.9 (1.6)
CHA_2DS_2-VASc, groups (%)		
CHA_2DS_2-VASc = 0	2.6	2.2
CHA_2DS_2-VASc = 1	7.6	6.5
CHA_2DS_2-VASc ≥ 2	89.7	91.3
Modified HAS-BLED score (mean ± SD)	2.5 (1.1)	2.6 (1.1)
Charlson Comorbidity Index (mean ± SD)	3.3 (2.8)	3.7 (3.0)
Hypertension (%)	85.7	88.2
Congestive heart failure (%)	36.3	37.4
Peripheral arterial disease (%)	11.7	11.8
Ischemic stroke (%)	6.5	6.8
Myocardial Infarction (%)	5.0	5.2
Diabetes mellitus (%)	36.0	36.4
Renal insufficiency (%)	17.9	23.5
Dementia/Senility (%)	10.4	21.8
Major bleeding (%)	4.5	4.2
Intracranial bleeding (%)	0.6	0.8
Gastrointestinal bleeding (%)	2.6	2.7
Ablation (%)	1.6	2.1
Cardioversion (%)	6.4	6.9
Antiplatelets (%)	18.5	14.6
VKA (%)	49.1	39.6
DOAC (%)	0.2	27.3
Beta-blockers (%)	68.4	72.4
Amiodarone (%)	4.6	4.8
Dronedarone (%)	0.6	1.0
Flecainide (%)	3.0	3.2
Propefanone (%)	1.1	0.6
Sotalol (%)	1.9	0.7

Temporal trends in antithrombotic therapy

Figure 2 shows the prescribing patterns in the 6 sequential AF patient cohorts. Use of antithrombotic therapy increased from 56% in 2011 to 69% of patients in 2016. This change was driven by the increase in use of DOACs while use of VKA decreased from 41 to 29%. In parallel, antiplatelet use decreased from 14 to 8%.

Antithrombotic therapy according to stroke risk

Figure 3 shows the use of antithrombotic therapy according to CHA_2DS_2-VASc score and cohort. For all cohorts the number of users of an antithrombotic therapy increased according to stroke risk. DOAC use increased between 2011 and 2016 in all stroke risk categories with the largest increase in patients with a CHA_2DS_2-VASc score of ≥ 2 (2011 0.7%; 2016 32.7%). There was a decline in the proportion of patients using VKA and antiplatelets across all stroke risk categories. The proportion of high risk patients not using any antithrombotic therapy decreased from 42.1% in 2011 to 28.6% in 2016.

The overall use of antithrombotic therapy increased in patients with low (CHA_2DS_2-VASc = 0) or moderate risk of stroke (CHA_2DS_2-VASc = 1) from 2011 to 2016, driven by an increase in the use of DOACs. The proportion of patients using VKA or antiplatelets as well as those not using any antithrombotic therapy decreased with the largest decline observed for VKA users (Fig. 3).

Factors associated with use of antithrombotic therapy

Figure 4 shows associations between risk factors and use of a specific antithrombotic therapy. In this analysis, patients who were users of DOAC, VKA and antiplatelets were individually compared against patients who did not use any antithrombotic therapy (reference group).

The effect of age slightly differed among considered therapies. For example, patients aged 75–84 and 65–74 were more likely to be users of DOAC, while patients at very advanced age more often used antiplatelets. Patients with a prior ischemic stroke were more often prescribed DOACs while patients with previous myocardial infarction were most frequently treated with antiplatelets. Patients who underwent catheter ablation or were treated with antiarrhythmic drugs were less likely to receive antithrombotic therapy.

Changes in antithrombotic therapy over time and stroke incidence

The adjusted stroke incidence rates decreased from 1.60 per 100 person–years in 2011 cohort to 1.21 in 2016 cohort

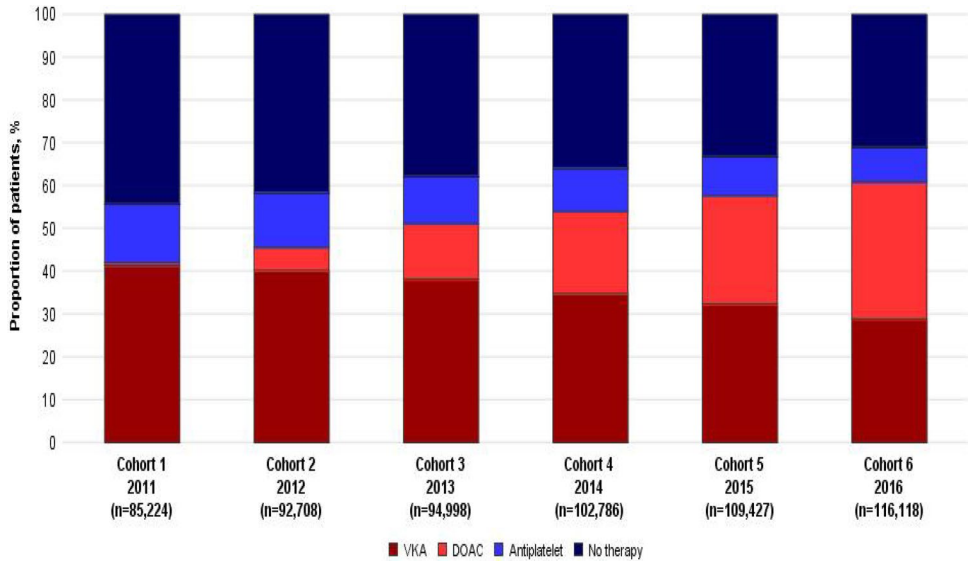

Fig. 2 Antithrombotic treatment by cohort

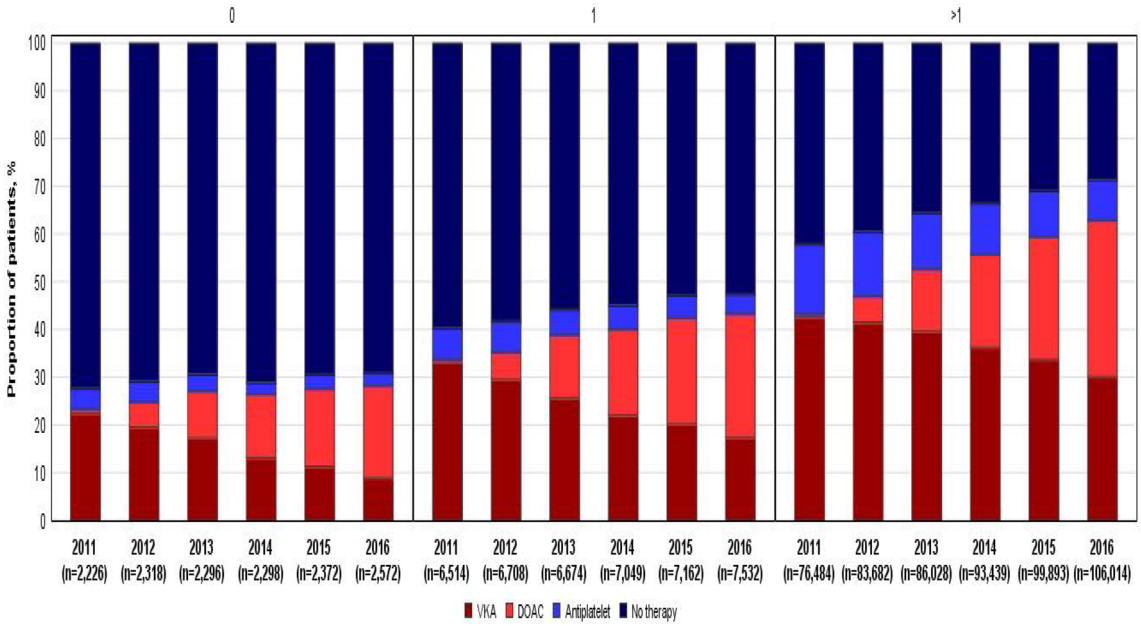

Fig. 3 Antithrombotic treatment by CHA_2DS_2-VASc score and cohort, for patients with a score of 0, 1, and > 1

(IRR: 0.76, 95% CI: 0.70–0.82) (Table 3). Risk for ischemic stroke declined from 1.42 per 100 patient years in 2011 to 1.06 in 2016 (IRR: 0.74, 95% CI: 0.68–0.81). Additional adjustment for OAC treatment resulted in an IRR for stroke of 0.82 (95% CI: 0.75–0.89). A similar pattern was observed for the outcome of ischemic stroke (IRR: 0.81, 95% CI: 0.74–0.89). There was no significant change in major and intracranial bleeding after adjusting for differences in patients characteristics in 2011 and 2016 cohort. A sensitivity analysis assessing outcomes over the year following the index year, i.e., in 2012 for the cohort 2011 and 2017 for the cohort 2016 yielded consistent results (Supplement Table S3).

Stroke and bleeding incidences according to age and stroke risk

Figure 5 displays the adjusted IRs of ischemic stroke and major bleeding stratified by age group and CHA_2DS_2-VASc score, respectively. This analysis revealed that the reduction in ischemic strokes was to a large extent driven by fewer strokes among elderly and high-risk patients. Regarding

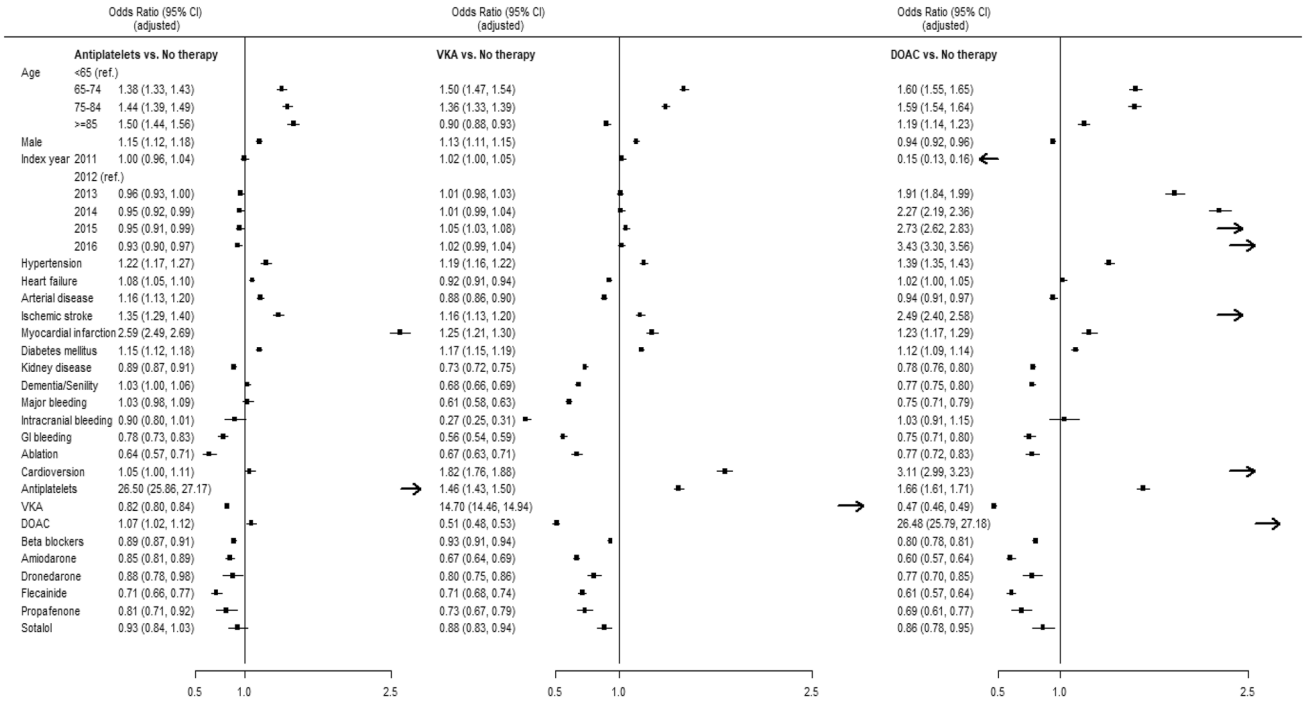

Fig. 4 Adjusted odds ratios with 95% confidence intervals associated with use of a specific antithrombotic therapy (antiplatelets, VKA, or DOAC) versus no use of an antithrombotic therapy

Table 3 IR and IRRs with 95% CIs for stroke and bleeding events

Outcomes	Cohort 2011 IR	Cohort 2016 IR	IRR (95% CI)
Effectiveness outcomes			
Stroke			
Crude	1.88	1.57	0.84 (0.78–0.90)
Adjusted for risk factors	1.60	1.21	0.76 (0.70–0.82)
Adjusted for risk factors and OAC treatment	1.51	1.23	0.82 (0.75–0.89)
Ischemic stroke			
Crude	1.68	1.38	0.82 (0.76–0.88)
Adjusted for risk factors	1.42	1.06	0.74 (0.68–0.81)
Adjusted for risk factors and OAC treatment	1.32	1.07	0.81 (0.74–0.89)
Hemorrhagic stroke			
Crude	0.26	0.26	1.00 (0.84–1.20)
Adjusted for risk factors	0.22	0.20	0.89 (0.72–1.10)
Adjusted for risk factors and OAC treatment	0.22	0.20	0.89 (0.72–1.11)
Safety outcomes			
Major bleeding			
Crude	1.88	2.09	1.11 (1.04–1.19)
Adjusted for risk factors	1.47	1.48	1.00 (0.93–1.09)
Adjusted for risk factors and OAC treatment	1.46	1.49	1.02 (0.94–1.11)
Intracranial bleeding			
Crude	0.54	0.61	1.14 (1.01–1.29)
Adjusted for risk factors	0.44	0.43	0.99 (0.85–1.15)
Adjusted for risk factors and OAC treatment	0.43	0.44	1.02 (0.88–1.19)

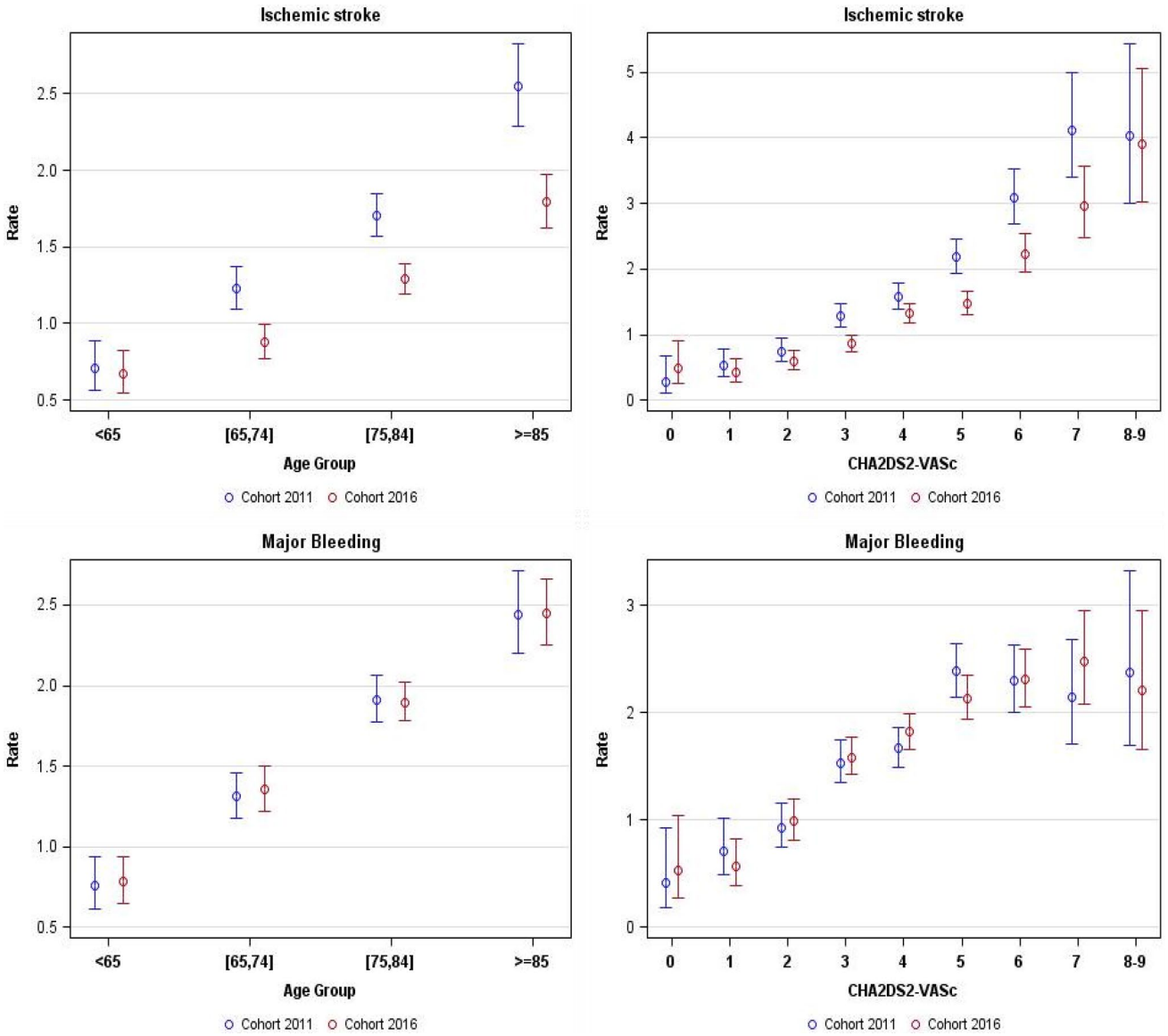

Fig. 5 Adjusted incidence rates with 95% confidence intervals of ischaemic stroke and major bleeding in cohorts 2011 and 2016, stratified by age group and CHA_2DS_2-VASc score

major bleeding, there were no significant differences between age groups or CHA_2DS_2-VASc scores (see Tables S4 and S5 in Supplement for details).

Discussion

Main findings

Our study reveals several important findings: (i) In a large unselected population of prevalent AF patients in Germany, the use of OAC increased from 42 to 61% between 2011 and 2016, mainly due to more frequent prescription of DOAC therapy; (ii) there is still significant underuse of OAC even in AF patients at high risk of stroke; (iii) although prescription of antiplatelet therapy is contraindicated by current guidelines, approximately 8% of AF patients were still receiving this therapy; (iv) in parallel with the increased prescription of OAC, particularly of DOACs, there was a significant decline in the incidence of strokes without an increase in bleeding complications.

Use of OAC therapy in prevalent AF over time

Our findings based on data collected over 6 sequential years demonstrate a considerable increase in prevalent AF, likely due to a true increase in prevalence and increased awareness for AF [10]. Over the same time period, a

significant increase in the rate of guideline-recommended anticoagulation therapy was observed. This change was predominantly due to increased use of DOACs, a finding which is in line with other observations [5–8]. Of note, the increase in DOAC use exceeded the decrease in VKA use suggesting that the introduction of DOACs is likely to have contributed to improved overall OAC rates among AF patients. These changes are also in agreement with the most recent ESC guidelines which prioritize DOAC therapy over other forms of OAC for stroke prevention in AF [11]. However, the present analysis also shows that the underuse of OAC therapy among AF patients in Germany is still common. This becomes particularly evident when OAC usage patterns were analyzed according to stroke risk, most importantly age. In all stroke risk categories, the use of DOACs increased over time mainly at the expense of VKA administration confirming previous similar findings [4–8, 12, 13]. Furthermore, 30–35% of patients with a CHA_2DS_2-VASc ≥ 2 are not treated with OAC despite their high risk. This is in contrast to data from prospective registries showing lower proportions of undertreated patients [4, 14]. This discrepancy may be due to significant bias within such registries (e.g., selection of expert centers, inclusion of non-consecutive patients, lack of auditing). The increased use of OAC therapy among very low risk patients (CHA_2DS_2-VASc = 0) may reflect the fact that the presence of AF and not the overall thromboembolic risk profile may be a primary driver of the administration of therapy for stroke prevention. Furthermore, AF patients may also have been prescribed OACs for transient purposes such as cardioversion or AF ablation.

Factors associated with OAC use

Findings from the multinomial logistic model evaluating factors associated with OAC use revealed that generally accepted stroke risk factors [15] were the main drivers of OAC use. Most notably, patients with history of stroke had in general a higher chance for treatment initiation, specifically with a DOAC, indicating preferential use of these substances for secondary stroke prophylaxis [16]. A history of myocardial infarction or advanced age were associated with a greater likelihood of antiplatelet use despite prior trials demonstrating superiority of VKA or DOAC therapy, especially in elderly subjects [17–21]. A rhythm control strategy, i.e., administration of antiarrhythmic drugs for stabilization of sinus rhythm or catheter ablation, was associated with a smaller chance of OAC intiation. Obviously, physicians still believe that rhythm control therapy justifies omitting OAC, for instance in patients with paroxysmal AF. Prior studies, however, have proven the opposite [22].

Association of increased OAC use and clinical outcomes

There are conflicting observations regarding clinical outcomes and increased use of OAC in patients with AF. Whereas several studies have reported a significant decline in AF-related strokes associated with more frequent OAC use [7, 8], other studies failed to do so [23–26]. Data from Sweden and England found that the increased OAC use contributed to a substantial reduction of ischemic strokes without increasing bleeding rates over 5–10 year intervals [7, 8]. A recent study from Germany using aggregated data from 2005 to 2014 found no correlation between the rise in OAC prescriptions and the number of strokes [26]. However, methodological limitations may explain this discrepancy. For instance, use of aggregated data does not allow to establish a direct relationship between AF patients and stroke episodes. Additionally, there was no adjustment for the increasing AF prevalence (e.g., age or comorbidities). Consistent with the above-mentioned studies, the present study demonstrates that the observed increase in OAC prescription - particularly using DOACs - was associated with a significant decline in stroke incidence. Specifically, our analysis showed an overall 24% incidence reduction in stroke between 2011 and 2016 which was mainly driven by reductions in ischemic strokes. This high risk reduction may predominantly be explained by increased OAC use, particularly the prescription of DOACs. Additional factors may have been operating such as the increased disease awareness. This might have yielded higher detection rates of AF in early disease stages and consequently to more dedicated therapy. Additional factors to explain the reduction in stroke incidence may be improved risk factor control, healthier lifestyles, and better management of preventive drug treatment in elderly patients [27].

Stratification for subgroups by age and CHA_2DS_2-VASc score demonstrated that patients with older age and high stroke risk benefitted most from the more wide-spread OAC therapy indicating that these frequently undertreated groups of patients can be reached by anticoagulants exhibiting an increased safety profile. Only for the combined group of patients with CHA_2DS_2-VASc score of 8 and 9 there was no significant risk reduction likely related to the low number of patients in these groups and lack of statistical power. In addition, as indicated from the results of multinomial logistic regression model, a disproportionately high rate of antiplatelets is still used in these patients limiting risk reduction. On the other hand, one could presume that with increased OAC use also the rate of bleedings would be higher. However, no increase in bleeding risk was observed between 2011 and 2016 despite much higher treatment rates. As the increased anticoagulation rate was mainly due to the increased use of DOACs, it can be assumed that this is primarily related to

the improved safety profile of DOACs compared to VKA [28, 29].

Limitations of the study

Our study has several limitations inherent to any study using claims data. The claims database lacks relevant information on INR values, body mass index, and laboratory data on renal function. Thus, detailed information on indications or contraindications in the clinical decision making for initiating or withholding antithrombotic treatment was not available. Another concern may be the potential for coding errors inherent to retrospective analysis of claims databases. Furthermore, the population covered by the database used in this study may not be generalizable beyond the statutory health-insured population in Germany, e.g., persons with private health insurance. However, the majority of the population in Germany is insured in the statutory health insurance. Finally, our study describes only an association between OAC uptake and incidence of AF-related strokes, but cannot prove causality.

Conclusion

Our observations in a large cohort of AF patients treated in Germany demonstrate an increased use of guideline-conform antithrombotic therapy in recent years, predominantly due to the more wide-spread use of DOAC therapy. This was associated with a significant decline in strokes without an increased incidence of bleeding complications.

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Compliance with ethical standards

Conflict of interest Professor Hohnloser has served as a consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo and Jansen. Professor Nabauer has received lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Dr. Basic is employee of Pfizer Deutschland GmbH. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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