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Real life anticoagulation treatment of patients with atrial fibrillation in Germany: extent and causes of anticoagulant under-use

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Abstract Oral anticoagulation (OAC) with either new oral anticoagulants (NOACs) or Vitamin-K antagonists (VKAs) is recommended by guidelines for patients with atrial fibrillation (AF) and a moderate to high risk of stroke. Based on a claims-based data set the aim of this study was to quantify the stroke-risk dependent OAC utilization profile of German AF patients and possible causes of OAC under-use. Our claims-based data set was derived from two German statutory health insurance funds for the years 2007–2010. All prevalent AF-patients in the period 2007–2009 were included. The OAC-need in 2010 was assumed whenever a $CHADS_2$- or CHA_2DS_2-VASC-score was >1 and no factor that disfavored OAC use existed. Causes of OAC under-use were analyzed using multivariate logistic regression. 108,632 AF-prevalent patients met the inclusion criteria. Average age was 75.43 years, average CHA_2DS_2-VASc-score was 4.38. OAC should have been recommended for 56.1/62.9 % of the patients (regarding factors disfavouring VKA/NOAC use). For 38.88/39.20 % of the patient-days in 2010 we could not observe any coverage by anticoagulants. Dementia of patients (OR 2.656) and general prescription patterns of the treating physician (OR 1.633) were the most important factors increasing the risk of OAC under-use. Patients who had consulted a cardiologist had a lower risk of being under-treated with OAC (OR 0.459). OAC under-use still seems to be one of the major challenges in the real-life treatment of AF patients. Our study confirms that both patient/disease characteristics and treatment environment/general prescribing behaviour of physicians may explain the OAC under-use in AF patients.

Keywords Oral anticoagulation · Atrial fibrillation · Anticoagulation under-use · Causes of anticoagulation under-use

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Introduction

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder [1]. It is associated with substantial lethality from stroke and thromboembolism [1–3]. Oral anticoagulation (OAC) with either new oral anticoagulants (NOACs) or Vitamin-K antagonists (VKAs) is recommended by guidelines for patients with a moderate to high risk of stroke, and either aspirin or no antithrombotic therapy is recommended for those at low risk of stroke [4–13].

Despite the established benefits of using OAC in AF patients, most studies show that the anticoagulant medication remains under-used [14]. A systematic review found

that almost 90 % of included studies showed a clear under-use of OAC, i.e. less than 70 % of the patients that were eligible for OAC treatment received OAC [15]. A recent claims-based data analysis measured OAC use for German AF patients on a daily basis. It concluded that, based on AF patients clearly indicated for OAC use in terms of stroke risk and possible factors disfavoring OAC use, at least 40.5 % of the observed patient days can be called under-use days. OAC was associated with a decreased stroke/thromboembolic event rate in this study [16].

The majority of the available data on OAC under-use have been gathered from prospective observational studies [15]. Potential patient inclusion bias and center cluster effects as well as small sample size are shortcomings of this study design [14, 15, 17]. Furthermore, in these studies it has often been impossible to perform a valid analysis of any causal factors associated with OAC under-use. This was regularly due to the overall low sample sizes, a patient/physician selection bias and data limitations in these studies. Furthermore, the minority of studies analyzed OAC usage of AF patients by taking factors disfavoring OAC use into account. Instead of that, OAC usage of all AF patients was examined leading to explanations for OAC under-use that may be or may not be in line with guideline recommendations [18]. Additionally, most studies dealing with causes of OAC under-use did not follow a multivariate causal research design; instead of that, only isolated causal factors were analyzed [19]. So the question why such a high number of AF patients eligible for OAC do not receive it remains open.

Based on an analysis of a large claims-based data set delivered by two German statutory health insurance funds, the aim of this study was to quantify the stroke-risk dependent OAC utilization profile of German AF patients in different scenarios as defined by different factors disfavoring OAC use. Furthermore, possible causes of OAC under-use both addressing patient-, disease- and physician-related factors should be identified.

Methods

Sample

Our claims-based data set was derived from two German statutory health insurance funds (AOK Plus; IKK Brandenburg und Berlin) which currently insure 2.9 million people or 4.15 % of the insured population by statute in Germany. A patient was included in our analysis if he or she received at least two outpatient or one inpatient diagnosis of AF in the period 2007–2009 (ICD10-Code I48.1-). Only patients aged 18 years or older and continuously insured between 01/01/2007 and 31/12/2010 were included. The years 2007–2009 were used as reference years, 2010 was used as observational period.

Risk factors and OAC use

We investigated whether patients who in principle needed OAC treatment were on OAC therapy in 2010 (365 days). On the basis of the available information in 2007–2009, the CHA_2DS_2-VASc-score [4, 5, 20] (Table A in Supplementary Material) was calculated for every patient in the sample. Score-related risk factors were assumed to be present whenever at least one outpatient or inpatient ICD-10 encoded diagnosis related to the CHA_2DS_2-VASc-score risk factors was documented. Whenever a CHA_2DS_2-VASc score >1 existed, it was assumed that there existed an OAC need [4, 5], as long as there existed no factor that disfavored the OAC use in that particular patient.

As none of the novel anticoagulants had been available in the observational period (01/01/2010–31/12/2010), only the use of vitamin K antagonists (VKA; Anatomical Therapeutic Chemical Classification (ATC)-code B01AA) could be identified. Furthermore, for descriptive reasons, we described the usage of heparins (ATC-code B01AB), aspirin (ATC-code B01AC06) and other antiplatelet drugs (ATC-code B01AC) in our sample.

Three scenarios were constructed to deal with factors disfavoring OAC use (Table B in Supplementary Material). We used the term "factors disfavoring OAC use" because not all of these factors can be called contraindications in the narrow sense of this word. Based on OAC product characteristics/labels, some of these factors like, for example, dementia or low adherence of the patient may potentially lead to the exclusion of an AF patient from OAC, but the final decision is the responsibility of the treating physician.

One scenario represented a broad spectrum of general factors based on the German summary of VKA product characteristics (here: Marcumar) [21]. The second scenario presented a similarly broad spectrum of general factors based on the German summary of NOAC products characteristics (here: Dabigatran) [22]. A third scenario was constructed as a combination of scenario 1 and 2. It represented patients which faced factors disfavoring VKA use without any factors disfavoring NOAC/Dabigatran use. The latter two scenarios were chosen because NOACs now present one of the OAC treatment options in AF patients and, provided that factors disfavoring the OAC use may be the main reason for OAC under-use, we aimed to show which additional patients may receive NOACs instead of VKAs because of a different safety profile of these drugs.

A patient was assumed to use OAC if a corresponding prescription was submitted to a pharmacy and, thus, passed on to the health insurance fund for reimbursement. As in an

earlier investigation [16], the use of OAC was classified for each of the 365 observed patient days into six alternative categories [10, 23].

I. Definite use of oral anticoagulation.
Category 1 Definite use of OAC; the observed patient-day was within the defined daily dose (DDD) range of the last OAC prescription (range = last prescription + DDD). Based on a WHO definition, the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [24].

II. Probable use of oral anticoagulation.
Category 2 The patient received at least one OAC prescription in 2010; the observed patient-day was beyond the DDD range of the last OAC prescription, but inside an additional period of 180 days. We called these additional 180 days "grace period". This grace period is in general accordance with practice documented in the literature [16, 25, 26]. We used 180 days to generate a relatively conservative estimate regarding OAC non-use days because VKA dosage between patients may differ.

III. Potential under-use of oral anticoagulation.
Category 3 The patient received at least one OAC prescription in 2010; the patient-day under consideration was beyond the DDD range of the last prescription, and outside a grace period of 180 days.
Category 4 The patient did not receive an OAC prescription in 2010, but received at least one for another anticoagulant or a heparin (ATC-Codes B01AC- excluding B01AC06 (aspirin) or B01AB-); the observed patient-day was within their specific DDD range of the last prescription plus a grace period of 90 days.
Category 5 The patient received neither an OAC prescription in 2010 nor one for another anticoagulant, but received a prescription for aspirin (ATC-Code B01AC06); the observed patient-day was within the DDD range of the last aspirin/other anticoagulant prescription plus a grace period of 90 days.

IV. Definite under-use of oral anticoagulation.
Category 6 The patient did not receive an OAC prescription in 2010. Furthermore, the observed patient-day was, regarding other anticoagulants and/or aspirin, either outside the DDD range of the last prescription plus a grace period of 90 days or none of the anticoagulants and/or aspirin was prescribed at all in 2010.

The number of patient-days in each of the six categories was calculated as a percentage of all patient-days and summarized in a descriptive analysis.

Causes of OAC under-use

A patient was defined as in need of OAC treatment if he or she had a CHA_2DS_2-VASc-Score >1 and there were no factors disfavouring an OAC use based on VKA product characteristics (Table B in Supplementary Material, first scenario). Consequently, analysis of OAC under-use causes was based on the VKA scenario regarding factors disfavouring OAC use only because only VKAs were available in the analysed observational period.

Patients were assigned as to be OAC under-use AF patients in two optional cases. (1) They were classified as OAC under-use patients if their observed patient days could not be assigned to either category 1 or 2 as defined above on more than 50 % of the relevant time in 2010. (2) In a more conservative approach they were classified as OAC under-use patients if none of the observed patient days could be assigned to either category 1 or 2 as defined above.

OAC under-use can stem from a variety of different factors. Known barriers to the use of OAC are logistical factors such as long travel distances to INR controls, sociodemographic characteristics of patients, patient-related factors including comorbidities, adherence of patients, alcohol abuse, type of AF, health care system related factors such as consultation of AF specialists/cardiologists and clinical risks associated with OAC use [15, 27, 28]. Based on an extensive review of literature, we identified 26 different factors potentially being able to predict OAC under-use (Table C in Supplementary Material). Because of data limitations, we could include 13 of them in our analysis; others were included by assuming that variables observable in our database correlate to these causal factors (e.g., physician behavior/knowledge as explained below). So, the following information available for each patient was finally included in our analysis:

- Age (as per 01/01/2010);
- Gender;
- Items included in the CHA_2DS_2Vasc-Score (based on 2007–2009: heart failure, hypertension, diabetes, stroke/TIA and myocardial infarction);
- Comorbidities, quantified by the Charlson comorbidity index (CCI) [29]. If at least one inpatient/outpatient diagnosis had been made of the diseases covered by the CCI and was documented in 2007–2009, it was taken for granted that the patient suffered from this disease;
- The number of prescribed active ingredients (excluding any antithrombotic agents) in 2009 if at least two prescriptions were dispensed by pharmacies (to exclude one-time medications);
- Any prescription of non-steroidal anti-inflammatory drugs (NSAID) in 2009/2010;

- Non-adherence/non-compliance of patients as measured by the prescription-based average medication possession ratio (MPR [30]) (01/01/2008–31/12/2009) related to the following medications which were the most frequent prescribed medications in the sample: torasemid, metoprolol, digitoxin, simvastatin, ramipril, bisoprolol, allopurinol, amlodipin, metformin, levothyroxine-natrium;
- Existence of prior intracranial/gastrointestinal bleedings in 2007, 2008, or 2009 (based on ICD-10 codes I60.-/I61.-/I62.-/K25/K26/K27/K28/K29.9/K31.82/K55.22/K57/K62.5/K66.1/K92.2);
- Dementia in 2007, 2008, or 2009 (based on ICD-10 codes F00/F01/F02/F03);
- Risk of falling in 2007, 2008, or 2009 (based on ICD-10 codes R26.-/R42.-);
- Any cancer disease in 2007, 2008, or 2009 documented by ICD-10 codes C-;
- Alcohol/drug abuse in 2007, 2008, or 2009 (based on ICD-10 codes F10.-/F11.-/F12.-/F13.-/F14.-/F15.-/F16.-/F17.-/F18.-/F19.-
- Paroxysmal AF in 2009 documented by ICD-10 code I48.10;
- Any inpatient surgery in 2009 or 2010 which may be related to a discontinuation of VKA usage;
- Any observable outpatient visit to a cardiologist in 2009;
- General prescription patterns of the treating general practitioner (GP): To describe OAC prescribing behavior of every GP, we observed medication therapy of all AF patients which were not included in our original analysis. Percentage of AF patients receiving at least one OAC prescription in 2009 as percentage of all these non-study AF patients was calculated for every GP. To describe prescribing behavior in a simplified way, we defined a "GP variable" as dummy variable that was "0" if the ratio as described above was above the average and "1" if that quota was below the average.

The possible predictors of OAC under-use were identified using multivariate logistical regression. Regression analysis was carried out using backward stepwise elimination to determine the most parsimonious factors associated with under-use probabilities. In the backward stepwise iterations, regression terms at a significance level of $p > 0.10$ were successively eliminated. All models were adjusted for age and gender. Patients without complete data (mainly, because the GP variable could not be calculated for every patient due to lack of other patients that were treated by these GPs or due to the fact that some patients were treated by more than one GP) were excluded from analysis. A significance level of 0.05 was chosen for analysis.

Table 1 Descriptive statistics of the whole sample and scenario samples

Variable	Continuously insured patients in 2007–2010 with at least 1 inpatient and/or 2 outpatient AF diagnoses in 2007–2009	Scenario A: CHA_2DS_2-VASc > 1 & NO factors disfavoring VKA (Marcumar) use	Scenario B: CHA_2DS_2-VASc > 1 & NO factors disfavoring NOAC (Dabigatran) use
N	108,632	60,941 (56.1 %)	68,340 (62.9 %)
Age in years[a]	75.43	75.00	75.71
Gender			
Female	55.7 %	57.3 %	58.0 %
Male	44.3 %	42.7 %	42.0 %
Total number of different drugs prescribed	6.38	5.75	5.83
$CHADS_2$ score	2.81	2.91	2.92
CHA_2DS_2-VASc score	4.38	4.55	4.56
Patients with ischemic stroke in 2009 (leading to hospital admission)	3,108 (2.86 %)	1,672 (2.74 %)	1,787 (2.61 %)
Patients with ischemic stroke in 2010 (leading to hospital admission)	2,134 (1.96 %)	1,026 (1.68 %)	1,078 (1.58 %)
Charlson Comorbidity Index[b]	5.57	5.00	4.98

[a] Based on 01/01/2010 (start of observational year)

[b] Score value 1: coronary artery disease (61.4 %), congestive heart failure (43.8 %), peripheral vascular disease (13.9 %), cerebral vascular accident (33.2 %), dementia (13.1 %), pulmonary disease (34.8 %), connective tissue disorder (10.7 %), peptic ulcer (6.9 %), mild liver disease (1.6 %), diabetes without complications (21.4 %); Score value 2: diabetes with complications (22.6 %); paraplegia (6.3 %); renal disease (23.4 %); any tumor/leukemia/lymphoma (22.9 %); Score value 3: moderate or severe liver disease (1.8 %); Score value 6: metastatic cancer (3.5 %); AIDS (0.3 %); age factor: 1 additional point for each decade ≥50 years of age

Results

Sample characteristics

We identified 108,632 AF-prevalent patients that met the inclusion criteria. Average age was 75.43 years and 55.7 % (60,475 patients) were female (Table 1). The average

Table 2 Patient days in the OAC use categories in three patient scenarios

OAC use categories						
	I. Definite OAC use	II. Probable OAC use	III. Potential OAC under-use			IV. Definite OAC under-use
	Category 1	Category 2	Category 3	Category 4	Category 5	Category 6
	At least one VKA prescription in 2010; observed day is inside of the DDD limit (since last prescription)	At least one VKA prescription in 2010; observed day is outside of the DDD limit, but within a grace period of 180 days (since last prescription)	At least one VKA prescription in 2010; observed day is outside of the DDD limit and outside of a 18 days grace period	No VKA prescription in 2010, but prescription for other anticoagulants/heparins (except ASS); observed day is inside the DDD limit (+90 days grace period) of that particular anticoagulant	No VKA prescription and no prescription of other anticoagulants/heparins in 2010, but prescription for ASS; observed day is inside the DDD limit (+90 days grace period)	No VKA prescription in 2010; observed day is not covered by other anticoagulants/heparin/ASS based on DDD and a grace period of 90 days since last prescription of these medications
A CHA_2DS_2-VASc > 1; no factors based on VKA product characteristics disfavoring OAC use						
60,941 patients with OAC need (22,243,465 days)	6,004,030 days (26.99 %)	3,871,881 days (17.41 %)	867,471 days (3.90 %)	1,042,769 days (4.69 %)	1,809,884 days (8.14 %)	8,647,430 days (38.88 %)
B CHA_2DS_2-VASc > 1; no factors based on Dabigatran product characteristics disfavoring OAC use						
68,340 patients with OAC need (24,964,905 days)	6,790,144 days (27.20 %)	4,356,114 days (17.45 %)	932,118 days (3.73 %)	1,082,884 days (4.33 %)	2,019,339 days (8.09 %)	9,785,003 days (39.20 %)

Observation period 01/01/2010–31/12/2010; number of patients: 108,632

Covered days; Number of patient days in the defined categories (as absolute numbers and as percentage of all patient-days); all patients were observed 365 days in 2010

Table 3 Patient characteristics of AF patients included in the causal research with/without OAC use

Variable	OAC under-use: case 1 (less than 183 of the observed days in category 1/2)		OAC under-use: case 2 (none of the observed days in category 1/2)	
	OAC use	OAC under-use	OAC use	OAC under-use
N	19,894	20,365	21,388	18,871
Gender (male/female)	47.85/52.15 %	38.27/61.73 %	47.37/52.63 %	38.06/61.94 %
Ø Age per 31.12.2009	74.10	76.16	74.12	76.30
Ø CHA_2DS_2VASc-score	4.53	4.57	4.54	4.56
Subset: CHA_2DS_2VASc-score = 2	1,986 (10.0 %)	2,035 (10.0 %)	2,127 (9.9 %)	1,894 (10.0 %)
Subset: CHA_2DS_2VASc-score = 3	3,552 (17.9 %)	3,651 (17.9 %)	3,796 (17.7 %)	3,407 (18.1 %)
Subset: CHA_2DS_2VASc-score = 4	4,794 (24.1 %)	4,658 (22.9 %)	5,151 (24.1 %)	4,301 (22.8 %)
Subset: CHA_2DS_2VASc-score = 5	4,352 (21.9 %)	4,500 (22.1 %)	4,687 (21.9 %)	4,165 (22.1 %)
Subset: CHA_2DS_2VASc-score = 6	2,895 (14.6 %)	2,964 (14.6 %)	3,122 (14.6 %)	2,737 (14.5 %)
Subset: CHA_2DS_2VASc-score > 6	2,315 (11.6 %)	2,557 (12.6 %)	2,505 (11.7 %)	2,367 (12.5 %)
Mean CCI	5.19	5.02	5.22	4.98
Mean nb. of prescribed RX 2009	5.65	5.05	5.65	5.00
Mean adherence (MPR)	67.68 %	67.26 %	67.68 %	67.22 %
Intracranial or gastrointestinal bleedings in 2007–2009	11.36 %	12.20 %	11.77 %	11.80 %
At least one dementia diagnosis in 2007–2009	8.44 %	19.57 %	8.82 %	20.03 %
At least one diagnosis regarding risk of falls in 2007–2009	10.87 %	12.75 %	10.98 %	12.77 %
At least one cancer diagnosis in 2007–2009	18.56 %	18.13 %	18.57 %	18.09 %
At least one diagnosis of alcohol or drug abuse in 2007–2009	7.17 %	7.93 %	7.34 %	7.80 %
At least one visit to a cardiologist in 2009	24.34 %	12.42 %	24.06 %	11.79 %
Paroxysmal AF diagnosis in 2009	17.71 %	20.21 %	18.16 %	19.90 %
At least one inpatient surgery in 2009 or 2010	25.23 %	23.67 %	25.96 %	22.72 %
Any prescription of NSAIDs in 2009/10	42.26 %	43.21 %	42.64 %	42.85 %
GP-based variable: percentage of patients being treated by a GP with under-average OAC prescribing behavior	53.92 %	65.82 %	54.20 %	66.45 %

CHA_2DS_2-VASc-score was 4.38, the average CCI was 5.57. 3,108 patients (2.86 %) experienced an ischemic stroke in the year before the observational period started, 2,134 patients (1.96 %) experienced an ischemic stroke during the observational period 2010.

OAC under-use

Based on the CHA_2DS_2-VASc-score, 107,457 (98.9 %) patients in the sample had a need for OAC. After consideration of the general factors disfavouring VKA use (Scenario A in Table 1), OAC should have been recommended for 60,941 patients (56.1 %). If factors disfavouring NOAC use were applied (Scenario B in Table 1), 68,340 patients (62.9 %) qualified for OAC.

Based on scenario A, 26.99 % of the analysed patient-days were definitely covered by OAC (Table 2, category 1). In 17.41 % of patient-days, anticoagulation use was probable, assuming a low OAC dosage, as we had allowed for a grace period of 180 days to cover very low dosages (Table 2, category 2). For 16.73 % of the patient-days, there was potential OAC under-use (Table 2, categories 3–5). Finally, for 38.88 % of patient-days, we could not observe any coverage by other anticoagulants, heparins, or anti-platelet drugs, respectively (definite OAC under-use; Table 2, category 6).

Based on the higher patient number in scenario B which includes less co-morbidities as factors potentially disfavouring OAC use, OAC usage numbers were comparable to scenario A (percentage of days): definite proof of OAC usage (category 1) 27.20 %, probable OAC use (category 2) 17.45 %, potential OAC under-use (categories 3–5) 16.15 %, and definite OAC under-use (category 6) 39.20 %.

Possible causes of OAC under-use

Based on the described OAC under-use analysis in scenario A, for a sample of 40,259 patients all possible causes of OAC under use, and specifically the GP variable, were observable. 20,365 of these patients (50.6 %) could be classified as OAC under-use patients because less than 184 days in 2010 could be assigned to either category 1 or 2 as defined above (case 1). In case 2, 18,871 patients (46.9 %) were classified as to be an under-use patient

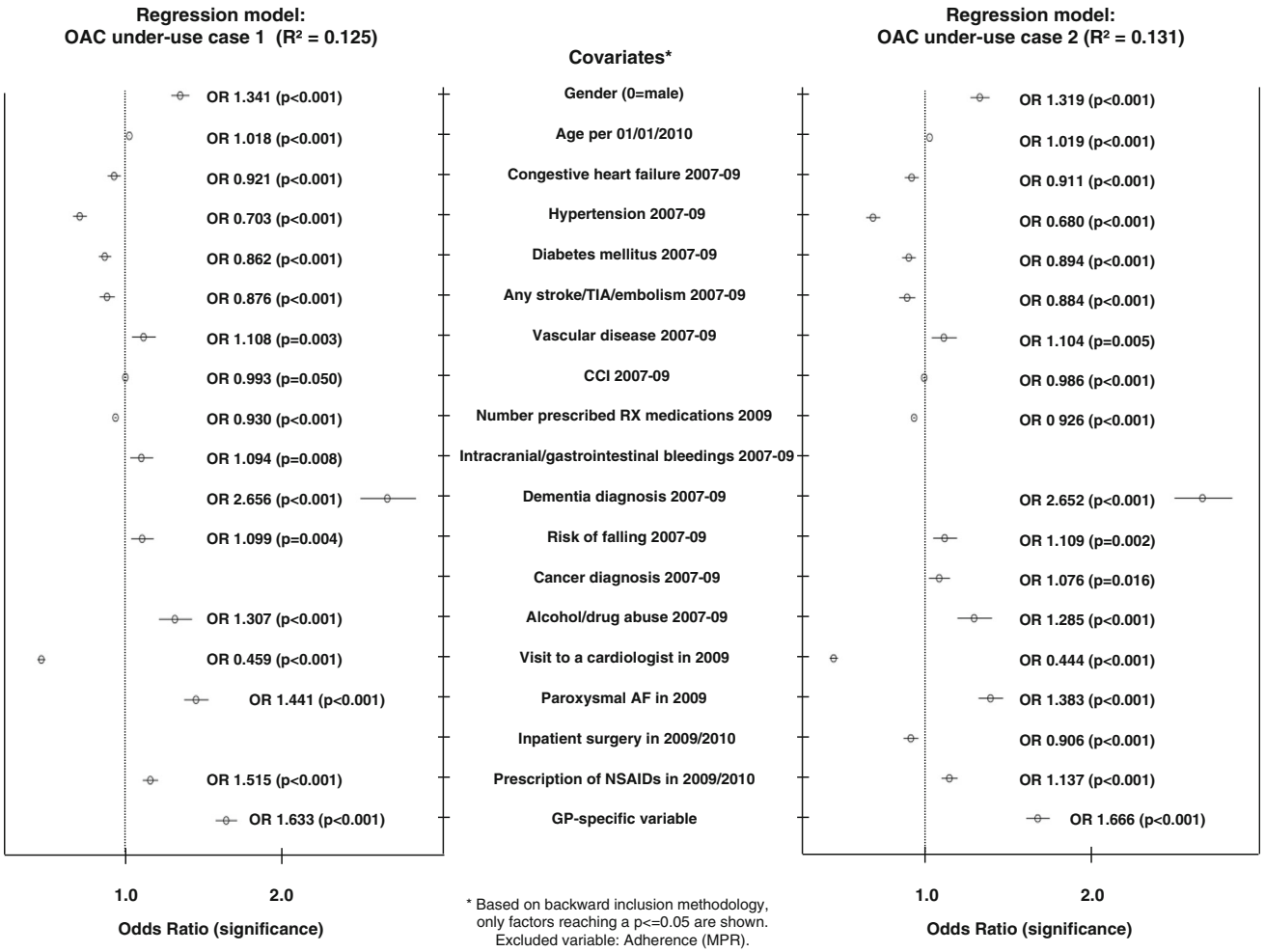

Fig. 1 Multivariate logistical regression models to estimate factors associated with OAC under-use in 2010

because none of the observed days could be assigned to either category 1 or 2 as defined above. Table 3 describes patient characteristics of OAC use/under-use patients in these two scenarios.

In our multivariate models (model 1 $R^2 = 0.125$; model 2 $R^2 = 0.131$), several variables associated with OAC under-use were identified (Fig. 1). Average adherence of patients as measured by the MPR related to Non-OAC treatment in 2008/09 could not exert any statistical relationship to OAC under-use ($p > 0.05$) and was thus excluded from the final model.

Based on those variables which proved to be significant in both models, age and gender showed an independent influence on OAC usage (older female patients face a higher OAC under-use risk). Furthermore, certain patient characteristics and co-morbidities proved important. Patients with congestive heart failure, hypertension, diabetes and/or with a history of stroke/TIA/embolism had a decreased risk of OAC under-use as well as the number of prescribed RX medications and the CCI (in one of the two models) decreased that risk.

On the other hand, the presence of a vascular disease increased the OAC under-use risk as well as prior bleedings did in one of the two models. Furthermore, dementia of patients, risk of falling, previous cancer (in one of the two models), documented alcohol/drug abuse, and prescription of NSAIDs in the present and/or previous year increased the OAC under-use risk as well as a diagnosis of paroxysmal AF. Futhermore, patients who had consulted a cardiologist in the previous year faced a considerably lower risk of being undertreated with OAC. Finally, the GP-specific variable indicates that the treatment decision is affected by the general prescribing behavior of the treating GPs.

Discussion

OAC use of analyzed AF patients

Based on an analysis of 108,632 AF patients, the first aim of this study was to quantify the stroke-risk dependent OAC utilization profile of German AF patients in different

scenarios as defined by different factors disfavoring OAC use. By using a day-based approach, it was even possible to detect non-adherence to OAC prescriptions [31]. Possible differences between the actual prescribed dose and the DDD were taken into account by means of rather long grace periods of 180 days (OAC) or 90 days (other anticoagulants or aspirin). As a second aim, we tried to identify possible causes of OAC under-use.

Our data show that 38.9–39.2 % of the observed days of AF patients with a CHA_2DS_2-VASc-score >1 and no present factors disfavouring OAC use can be called days of definite OAC under-use. Based on our definition of OAC under-use patients (none of the observed days in categories 1/2 or, alternatively, less than 50 % of observed days in categories 1/2), 46.9–50.6 % of AF patients may be called OAC under-use patients. Our results confirm the results of previous studies. A recent German claims-data analysis reported a percentage of 40.5–48.7 % OAC under-use days. Our figures are also comparable to available international publications [17, 32, 33] and the already cited systematic review that found that almost 90 % of included studies showed a clear under-use of OAC [15]. So, OAC under-use still seems to be one of the major challenges in the real-life treatment of AF patients.

Causes of OAC under-use

The main strength of our study is the very detailed analysis of possible causes of OAC under-use. We analysed a patient sample that was clearly indicated for OAC use in terms of stroke risk and non-presence of any factors disfavouring OAC use. Or study confirms that both patient/disease characteristics and factors describing the treatment environment/general prescribing behaviour of physicians may explain the OAC under use in AF patients.

We confirm the results of previous studies that age and gender influence the OAC usage. In line with previous data, older female patients faced a higher OAC under-use risk in our sample [16, 19, 34, 35]. However, we cannot confirm that adherence of AF patients' influences the OAC usage rate as was shown in other studies [15, 36]. This may be due to the fact that we were only able to measure adherence as average MPR related to the most common prescribed Non-OAC drugs in our AF patient sample. The MPR may be a weak indicator of the true adherence of AF patients. On the other hand, most studies showing that non-adherence is related to OAC under-use measured adherence based on physicians statements regarding adherence of their patients [37–39]. However, existing data show that evaluation by physicians is not necessarily an effective indicator of patients' adherence [40, 41].

Our data show that the comorbidity profile of patients influenced OAC usage. A higher number of prescribed RX medications and, at least in one of the models, a higher CCI decreased the OAC under-use risk. This pattern was not described in previous publications. It may be related to the fact that patients with several RX medications visit their treating physicians more often than other patients do. That may ease the necessary INR value management associated with a VKA-based OAC. We also identified congestive heart failure, diabetes, and hypertension as factors decreasing the probability of OAC under-use; the latter was reported by an earlier study as well [34]. Treating physicians may see these diseases as additional stroke risk factors that increase the OAC need. On the other hand, the presence of a vascular disease increased the OAC under-use risk in our study. A similar pattern was reported in an earlier study that showed that heart failure was correlated to an under-average OAC use [34].

We also identified a relationship between the risk of falling, any dementia and alcohol/drug abuse and an increased OAC under-use risk. This is in line with earlier study results [18, 39, 42], and guideline recommendations which recommend OAC use in cases of falling risk/dementia/alcohol and/or drug abuse only if treating physicians believe that the OAC is beneficial despite the existing patient-related risks [4, 20].

Our study showed that, at least in one of the models, a previous cancer diagnosis in an AF patient increases the OAC under-use risk [38, 43]. Based on existing guidelines, long-term anticoagulation with low-molecular heparins (LMWH) is recommended in cancer patients [44]. So, a lower OAC usage rate and a higher LMWH usage rate could be expected. However, in a subgroup analysis covering OAC-eligible AF patients with a previous cancer diagnosis only, we still observed 35.2 % of definite OAC under-use days (category 6) which means that these days were neither protected by VKA nor by other anticoagulation drugs including heparins. Days protected by LMWH (±90 days grace period) constituted 6.5 % of all observed days for the whole included AF group and 9.1 % of the days of the AF-cancer subgroup.

The prescription of NSAIDs in the present and/or previous year while/before the observation increased the OAC under-use risk in our study. This result, which was already observed by other studies [37, 45], may be related to the fact that NSAIDs in combination with OAC increase the bleeding risk. This may lead to the decision not to use OAC in AF patients. We also confirm the observation of previous studies that a diagnosis of paroxysmal AF is related to less OAC use [18, 34, 37]. Whereas guidelines do not differ between types of AF in terms of OAC usage recommendations, treating physicians obviously still see OAC as treatment for patients with more frequent/permanent AF.

Finally, as expected and known from previous studies, a history of stroke increases the probability that an AF patient receives OAC [34].

It is known from several studies that both physicians' knowledge and beliefs may influence OAC prescribing behavior [42, 46, 47]. However, most of these studies analyzing these factors were based on physician survey- or smaller observational study designs which did not control for patient characteristics. Only few studies dealing with large AF patient samples did analyze patient-related and physician-related factors potentially explaining OAC under-use in a simultaneous multivariate analysis so far. In our study which followed such a broad approach we could show that both the visit of a cardiologist in the previous year and the general prescribing behavior of the treating GP influence the OAC use rate in AF patients. Specifically, if a treating GP was known to prescribe OAC with an under-average probability in other AF patients, this fact also increased the OAC under-use risk in our sample.

Limitations

The authors acknowledge some limitations of the study. First, due to limited data availability, we could not analyze all factors potentially explaining OAC under-use (Table C in Supplementary Material). Mainly, factors describing knowledge/beliefs of physicians/patients, but also potential difficulties with INR management and previous negative experiences with OAC which were not documented in our claims database were not included. Nevertheless, our study is one of the few publications that, besides establishing an OAC under-use rate, also quantify causes of OAC under-use in a multivariate and comprehensive analysis.

Second, as it is common with claims-based data studies, its weakness lies in the fact that these data were primarily collected for the purpose of financial claims and not gathered specifically for research purposes. Limitations are present in both the level of detail and precision. Several data on potentially contributing or confounding risk factors regarding OAC use were not available. For example, INR values were not available. Nevertheless and despite these weaknesses, existing investigations show that claims-based data sets can be used as valid research data [48, 49]. In addition, our data are not subject to the possible patient selection biases or cluster effects that may have influenced previous investigations. In Germany, about 85 % of the population are insured in public statutory insurances. Our data were derived from one large and one small insurance fund. Consequently, patient selection bias is not a concern. Our data may be affected by a regional bias because our sickness funds insure patients in only four out of 16 German states. However, due to the uniform health insurance system in Germany we do not expect that this potential bias may systematically influence our study results.

Third, our medication analysis only included medications covered by the insurance funds providing the data. In the German market, OAC and other anticoagulants are only available through a prescription. Once these have been turned in by patients they are included in our dataset. However, aspirin may be obtained by patients over the counter: data about over the counter medications were not available. In an analysis covering a large AF sample in UK, it was concluded that among patients not prescribed an OAC, about 80 % were prescribed an antiplatelet drug [19]. We cannot confirm this observation which may be explained by the fact that several OAC under-use patients obtain aspirin out of pocket.

Fourth, the grace periods we defined in determining the anticoagulation status of a patient-day (180 for VKA; 90 days for other anticoagulation treatment or anti-platelets) are random, but in accordance with practice documented in the literature [16, 25, 26]. We used 180 days to generate a relatively conservative estimate and to be sure that a patient-day could be considered as characterized by under-use.

Fifth, we analysed an exceptionally old and comorbid sample with an average CHA_2DS_2-VASc-score of 4.38 and an average CCI of 5.57. Because age is an independent predictor of OAC under-use this may have led to an overestimation of the percentage of OAC under-use patients. On the other hand, because of the rising life expectancy in most industrialized countries [50], our study may describe a treating environment that becomes reality in near future.

Sixth, due to our large sample size, some independent variables may exert a significant statistical influence in our multivariate analysis regarding causes of OAC under-use without having a clinical importance because of low effect sizes. In order to address this potential limitation, we analyzed these causes in two different scenarios. Nevertheless, it is possible that some factors have been identified as statistically significant OAC under-use causes but, due to low odds ratios, cannot be called causal factors in a clinically meaningful way.

Conclusions

Our data show that OAC under-use is still common in AF patients even if stroke risk and factors potentially disfavouring OAC use are taken into account. The comorbidity profile of patients as well as certain sociodemographic patient characteristics at least partly explain OAC under-use. Whereas cardiologists more often recommend OAC, GPs obviously differ in their view on benefits and harms of OAC. This still leads to an under-treatment of AF patients

in GP practices known to undertreat all their other AF patients. Other studies have shown that this OAC undertreatment finally leads to a higher stroke/thromboembolic event risk of AF patients [16].

Whether the recent introduction of NOACs improved the situation needs to be seen in future. Our results indicate that even with newer anticoagulants on the market it is still necessary to promote anticoagulation therapy, especially among GPs which treat the majority of AF patients in many countries.

Conflict of interest Matthias Pfannkuche is employed by Boehringer Ingelheim Pharma (Germany). Thomas Wilke has acted as consultant for Boehringer Ingelheim Pharma, Bayer, GSK, LEO Pharma, Novartis, and BMS, and Pharmerit International. Ulf Maywald, Andreas Fuchs and Oliver Harks work for one of the insurance funds providing the data or their data warehouse providers (AOK Plus: Maywald/Fuchs; GWQ ServicePlus AG: Harks).

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