Trends in Atrial Fibrillation and Prescription of Oral Anticoagulants and Embolic Strokes in Germany

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ABSTRACT

Background: The aim of the study was to compare trends in frequency of atrial fibrillation (AF) with the prescription rates of oral anticoagulants (OAC) and the incidence of embolic stroke (ES) from 2005 through 2014.
Methods: Annual numbers of hospitalized patients with AF and ES were extracted from the Federal Bureau of Statistics. Defined daily doses (DDD) of prescribed OAC among outpatients were extracted from the insurance drug information system.
Results: The number of cases hospitalized with the diagnosis AF increased continuously by 78.3% (1.25 Million in 2005 to 2.19 Million in 2014, $p < 0.001$), likewise frequency of ES increased by 89.0% (from 46,068 to 87,050, $p < 0.001$) and the number of prescribed DDD of OAC almost doubled by 105.4% (from 271,328 to 557,281, $p < 0.001$). There is an almost linear correlation between occurrence of AF and ES ($R^2 = 0.9683$). In contrast association between prescription rate of OAC and incidence of ES is not linear as there was a disproportional increase in OAC prescriptions beginning in the year 2010 that is not accompanied by a reduction of cases hospitalized with ES.
Conclusions: Our analysis of drug treatment rates for OAC in outpatients and hospitalization rates for ES revealed a disproportional increase in prescription of OAC beginning in the year 2010 that does not affect the number of cases hospitalized with ES.

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1. Introduction

Apart from atherosclerosis, arterial embolism is the main cause of cerebral infarction. Atrial fibrillation (AF) has been recognized to be most relevant pathology associated with embolic stroke (ES) and there has been much effort taken to prevent embolic stroke by implementing a consequent anticoagulation strategy in the case of AF in the recent years [1,2]. Furthermore it is known that a stroke in patients with AF is more severe and the outcome significant worse than in patients with sinus rhythm [3]. Oral anticoagulation (OAC) with direct new oral anticoagulants (DOAC) or Vitamin-K antagonists (VKA) is recommended by guidelines for patients with AF and a moderate to high risk of stroke [4–6]. Despite these recommendations ES is still of increasing relevance in different health systems. Data from a Canadian urgent transient ischemic attack clinic in Ontario reported that the proportion of ES increased from 26% to 56% during the period of 2002 to 2012 ($p < 0.05$) [7].

An increasing number of patients with AF and an underuse of OAC are discussed as main reasons for the increasing figure of ES. Analysis of the Framingham cohort over 50 years reported an increase of the age-adjusted prevalence of AF per 1000 person-years (from 12.6 in 1958–1967 to 25.7 in 1998–2007 in men, $p = 0.0007$; from 8.1 in 1958–1967 to 11.8 in 1998–2007 in women, $p = 0.009$) [8]. Accepting an indication for OAC in cases with a CHADS2- or CHA2DS2-VASC-score >1 a German study based on a claims-based data set from two statutory health insurance funds for the years 2007–2010 reported that 38.88% and 39.20% respectively, of observed patient-days were not covered by anticoagulants [9]. An analysis of the administrative health data registry of the Stockholm region reported better adherence to warfarin and apixaban than to dabigatran or rivaroxaban in regular care [10]. A growing rate of total OAC prescriptions is expected to continue because DOAC are given preference over warfarin in guidelines on stroke prevention in patients with atrial fibrillation, because of growing physician experience, and emergence of potential new indications [11].

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The aim of this study was to compare nationwide trends in frequency of AF, prescription rates of OAC and incidence of ES in Germany from 2005 to 2014.

2. Methods

Hospitals in Germany annually transfer their individual hospitalization data, including one primary diagnosis, up to 89 secondary diagnoses coded by ICD-10 (International Classification of Diseases, 10th edition), and up to 100 medical procedures according to a national classification of operations and procedures to the Institute for the Hospital Renumeration System (InEK). After a plausibility control, the InEK forwards anonymized data to the Federal Bureau of Statistics. Principles of the analysis of this hospitalization file have been published several times previously [12,13]. We identified all hospitalizations of the years 2005 through 2014 that included the ICD-codes covering the field of AF (I48, *principal and additional diagnosis) and strokes (I63, *principal diagnosis only) by calendar year, sex, and 5-year age group.

Roughly 90% of the population in Germany are statutorily insured and entitled to receive health promotion and disease prevention benefits to maintain and restore their health or to improve their state of health. The statutory health insurance (SHI) is funded by the statutory health insurance funds which, being public-law corporations, are financially and organizationally independent.

The statutory health insurances provide regular reports of the SHI-drug information system according to a German law regulation (§302 SGB V). These reports are based on billing data from all statutory health insurance companies in Germany. For data confidentiality, all data are anonymized. Detailed lists of all anticoagulants and anti-platelet agents (APA) in the years 2005 to 2014 were provided by the WIDO (Wissenschaftliche Institut der AOK) which is a scientific institute of the statutory health insurance AOK but these lists included data from all statutory health insurance companies in Germany.

3. Statistical methods

For AF we considered any case with the principal and the additional diagnosis of I48 in the years 2005 to 2014. For strokes we considered only cases with the principal diagnosis I63 including the subtypes as coded by the last digit. Based on the data provided by WIDO, we analyzed the prescription time trend of all OAC in Germany from 2005 to 2014. As we compare hospitalization rates of AF and ES considering the whole German population with prescription rates of OAC outside the hospitals considering the 90% of the German population prescribed to outpatients who are insured by the statutory health insurance system our analyses is just descriptive. Due to this two different data bases we did not analyze statistical significance. Calculations were done using Microsoft® Excel 2003 and Microsoft® Access 2003. R 3.1.0 was used to perform linear regression models to estimate linear time trends.

4. Results

4.1. Atrial fibrillation

The total number of cases with the principal or additional diagnosis AF increased continuously from 1.25 Million in 2005 to 2.19 Million in 2014 ($+75.8$, $p < 0.001$) (Table 1, Fig. 1). Most of these diagnoses were coded as additional diagnosis. The rate of those with the principal diagnosis AF that can be assumed to be hospitalized for AF treatment primarily increased from 180,000 in 2005 to 289,000 in 2014 ($+60.6$ $p < 0.001$).

4.2. Stroke

The total number of strokes increased from 185,014 in 2005 to 244,761 in 2014 ($+32.2\%$, $p < 0.001$) (Table 1, Fig. 1). Most of these strokes were coded as non-ES. Such non-ES increased by 13.5% only in the period from 2005 to 2014 whereas the ES increased by 89.0%. Considering population based data per 100,000 there is an almost linear correlation between AF and ES ($R^2 = 0.9683$).
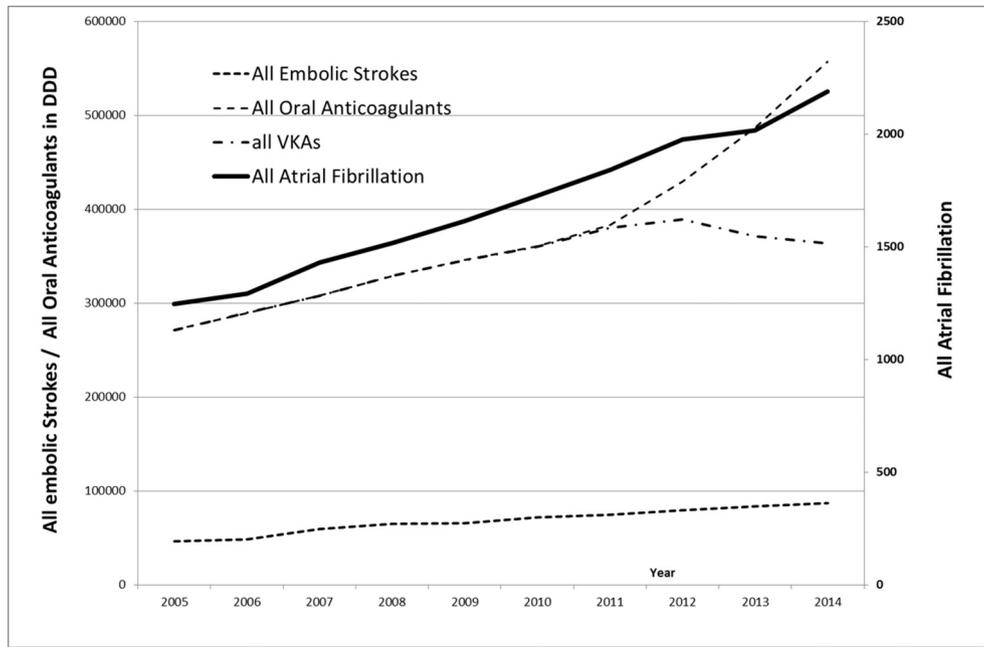
4.3. Oral anticoagulants

The number of DDD of OAC increased from 2005 by 105.4% (from 271,328 in 2005 to 557,281 in 2014, $p < 0.001$) (Table 2, Fig. 1). This increase can be divided into two periods. From 2005 to 2011 there was a continuous but slower increase compared to the years 2012 to 2014. Mean increase of DDD each year in the period from 2005 to 2011 was $18,675 \pm 3010$. Thereafter the yearly increase of DDD was $57,969 \pm 12,280$. Prescription of VKA increased till 2012. Thereafter the increasing prescription of OAC is only driven by DOAC.

Table 1

Listed are the numbers of all cases hospitalized with the principal or additional diagnosis atrial fibrillation and all cases with the principal diagnosis stroke separate for the different types of stroke in Germany in the period from 2005 to 2014. For all cases with AF and ES we include population based frequency per 100,000 inhabitants according to the German standard 2011.

	ICD-code	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Delta
Atrial fibrillation (×1000)												
Additional diagnosis	I48.-	1066	1130	1224	1297	1384	1475	1578	1700	1736	1901	78.3%
Principal diagnosis	I48,-	180	190	207	218	231	250	262	276	279	289	60.6%
All	I48,-	1246	1293	1431	1515	1615	1725	1840	1976	2015	2190	75.8%
All per 100,000	I48,-	1433	1487	1591	1654	1737	1829	1969	2094	2116	2276	58.8
Stroke (principal diagnosis only)												
Thrombosis of precerebral arteries	I63.0	4057	5275	6469	7684	8201	8851	9610	10,002	11,651	12,095	198.1
Embolism of precerebral arteries	I63.1	3754	4165	4795	5096	4705	6050	5990	6457	7003	7378	96.5
Unspecified occlusion or stenosis of precerebral arteries	I63.2	5840	6227	6007	5946	5975	6553	6592	6506	6609	6705	14.8
Thrombosis of cerebral arteries	I63.3	35,628	38,544	41,720	46,540	48,093	49,992	50,013	52,518	53,419	54,218	52.2
Embolism of cerebral arteries	I63.4	42,314	44,500	54,672	59,929	61,121	65,697	68,635	72,739	76,256	79,672	88.3
Unspecified occlusion or stenosis of cerebral arteries	I63.5	59,780	61,349	58,496	56,345	55,559	55,143	56,359	53,459	51,861	49,401	−17.4
Cerebral venous thrombosis, nonpyogenic	I63.6	126	172	207	185	171	192	180	156	176	192	52.4
Other	I63.8	16,587	14,270	15,112	16,311	18,207	19,998	20,747	22,794	21,669	21,875	31.9
Unspecified	I63.9	16,928	25,076	22,686	21,321	20,671	17,317	15,967	14,764	13,428	13,225	−21.9
All strokes	I63.-	185,014	199,578	210,164	219,357	222,703	229,793	234,093	239,395	242,072	244,761	32.3
All embolic strokes	I63.1 + I63.4	46,068	48,665	59,467	65,025	65,826	71,747	74,625	79,196	83,259	87,050	89.0
All embolic strokes per 100,000	I63.1 + I63.4	63	65	78	84	84	89	92	97	100	103	63,4

ICD indicates International Statistical Classification of Diseases; ES indicates embolic stroke.

Fig. 1. Number of all hospitalized cases with atrial fibrillation and all cases with embolic strokes and number of all DDD of oral anticoagulants prescribed each year in Germany in the years from 2005 to 2014.

5. Discussion

The present data show an increase in prescription of OAC beginning in the years 2011 and 2012 that is not accompanied by a reduction of cases hospitalized with ES.

Exact incidence and prevalence data of AF in Germany are not available. Based on the population-based Gutenberg Health Study prevalence of AF, weighted for age and sex distribution of the general population, was 2.5%. AF was found to be more common in older persons, with a more pronounced increase in men: whereas its prevalence was 0.7% in 35- to 44-year-old men, the corresponding figure for the age group 65 to 74 was as high as 10.6% [14]. In contrast to these population-based data we used the number of hospitalized cases with the principal and additional diagnosis of AF. Hospitalization for a specific disease is not influenced by their incidence only but also by the general effectiveness of the available therapy and the infrastructure of the local health system. Thus our data might underestimate the cases of AF but represent the burden of AF in the German population and not the exact number which is unknown. It has to be considered that each case does not necessarily represent one single person and not everybody suffering from AF got hospitalized each year. For ES we included cases with the principal diagnosis only. As a stroke is a clinically relevant event there is a high probability that all cases

represent a clinical symptomatic stroke. Due to the regulation for DRG-coding readmission of a patient with a stroke can only have the principal diagnosis stroke again, if a new stroke occurs. Thus, the included cases with the principal diagnosis ES can be accounted to be representative for the burden of ES in Germany.

We do not have exact population based incidence rates our analysis showed a strong linear correlation between hospitalized cases with AF and ES. Although the linkage between ES and AF is not fully understood yet and about 30% of all embolic strokes are classified as cryptogenic, our finding is in line with the literature and the pathophysiologic understanding of AF and ES.

The steeper increase of prescriptions rates of OAC starting in the years 2011 might have different reasons. First, the CHA2DS2-VASc score for a more detailed stroke risk assessment in patients with a CHADS2 score of 0–1 was recommended in the 2010 Guidelines for the management of atrial fibrillation of the European Heart Society for the first time [5]. Use of the CHA2DS2-VASc score should significantly improve classification of AF patients at low and intermediate risk of stroke, compared to the commonly used CHADS2 score [15]. Second, DOAC became available in Germany in 2008 with the introduction of rivaroxaban and dabigatran and got a first-line treatment recommendation in the 2012 update of the 2010 Guidelines for the management of atrial fibrillation of the European Heart Society [6]. Both

Table 2
Listed are the numbers of all OAC prescribed in Germany the period from 2005 to 2014 in 1000 DDD.

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
All VKA + all DOAC	271.328	289.546	307.919	328.777	345.820	360.265	383.375	429.616	486.546	557.281
Increase each year		18.218	18.373	20.858	17.043	14.445	23.110	46.241	56.930	70.735
All VKA	271.328	289.546	307.919	328.755	345.620	359.780	380.295	389.107	371.374	363.713
Phenprocoumon	269.050	287.026	305.158	325.698	342.230	356.104	376.283	385.071	367.545	359.963
Warfarin	2.278	2.520	2.761	3.057	3.390	3.676	4.013	4.035	3.828	3.750
All DOAC				22	199	485	3.080	40.510	115.173	193.568
Rivaroxaban				6	149	358	684	25.495	83.375	134.541
Dabigatranetexilat				16	50	127	2.393	14.976	27.467	34.317
Apixaban							3	39	4.330	24.710

VKA indicates Vitamin K antagonist; OAC indicates oral anticoagulation; DOAC indicates direct oral anticoagulation; DDD indicates defined daily dose.

recommendations intend to reach more patients at risk for ES and to reduce the number of ES.

The change form CHADS2 score to CHA2DS2-VASc score increases the rate of patients with AF that should have OAC from 66% (1156 from 1733 have >1 point, Gage 2001) to 94% (6906 of 7329 have >1 point, [16]) and especially more patients with lower risk of ES are affected. The 2010 ESC guidelines support patients with 'moderate risk' (currently defined as CHADS2 score = 1, i.e. one risk factor) still derive significant benefit from OAC over aspirin use, often with low rates of major hemorrhage [5]. According to this assumption our analysis should have shown that with a steeper increase in prescription of OAC the number of cases hospitalized with the principal diagnosis ES should decrease. But, this seems not to be true in Germany. Despite a disproportional higher prescription of OAC in the years 2012 to 2014 compared to the years 2005 to 2011 there is an unchanged linear increased in ES cases. One can argue that without the increasing prescription of OAC there could have been an increase in hospitalized ES cases due to the greying German population which is prevented by the higher prescription rates. All effects of the greying population should also have influenced the hospitalization rates associated with AF. We do not see such an effect. Hospitalization rates for AF and ES increased continuously and showed a strong correlation which is not affected by the steep increase in prescription of OAC in the years 2012 to 2014. We are not aware of other publications reporting similar data. There is a recent report from UK that reported that the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Trial, published in 2017, provided strong evidence of the effectiveness of warfarin at age ≥80 years, but the impact on incidence of AF-related stroke and peripheral embolic vascular events is uncertain. They studied age-specific incidence and outcome of all AF-related incident strokes and systemic emboli from 2002 to 2012 in the Oxford Vascular Study again and found no reduction in incident AF-related events after 2007 at all ages. A third of all disabling/fatal strokes occur in non-anticoagulated patients with known prior AF [17].

Thus, we conclude that the steep increase in prescribed DDD of OAC prescribed in the years 2012 to 2014 does not directly affect the hospitalization rates for ES. The change from CHADS2 to CHA2DS2-VASc score and the trust in the safety of the DOACs [18–20] led to a widespread prescription of DOAC but not yet to a measurable effect on hospitalization rates for ES.

6. Strength and limitations

A major strength of this study is the large data set which includes virtually all German hospitals and the observation period of 10 years. This allows a unique view at the current clinical practice. Moreover, to the best of our knowledge, there is currently no other publication addressing this topic from a population based viewpoint in Germany.

There are a few limitations to this study. This observational study is based on retrospective hospital data. As we used routine hospitalization data, we were not able to fully address potential confounding as indications for treatment, quality of treatment, polypharmacy with combined treatment with OAC and APA or relevant comorbidities. In addition we are not able to differentiate the effect of different DOAC. Although we listed the absolute numbers of DDD in Table 2 a drug specific linkage to ES of bleeding is not possible. It has to be pointed out that the analysis is based on cases and not on individual patients. As a consequence, a patient could be included several times in the statistics if he had embolic events at two different times within one year.

Although DRG data are frequently used for secondary purposes, there is no systematic analysis of coding quality in Germany and the agreement of coding and "reality" has yet to be investigated in representative studies. Therefore, we cannot assess if and how coding errors may have impacted our analysis. Thus, we do not actually know how the differential diagnosis of the embolic event is validated in each case.

7. Conclusions

Our ecologic nationwide analysis of drug treatment rates for OAC in outpatients and hospitalization rates for ES revealed a disproportional increase in prescription of OAC beginning in the year 2010 that is not accompanied by a reduction of cases hospitalized with ES.

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