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Increasing use of anticoagulants in Germany and its impact on hospitalization for gastrointestinal bleeding

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ABSTRACT

Objectives: The aim of the study was to compare nationwide time trends of oral anticoagulant prescriptions with the time trend of gastrointestinal bleeding (GIB) in Germany from 2005 through 2016.

Patients and methods: The annual number of hospital admissions for GIB associated with gastric ulcers, duodenal ulcers, hematemesis, melena, hematochezia, and unspecified gastrointestinal bleeding (USGIH) was taken from the nationwide hospital referral file by the Federal Bureau of Statistics. The hospitalization rates were age-standardized using the German Standard Population 2011. The defined daily doses (DDD) of prescribed anticoagulants in outpatients for the same calendar period were taken from reports of the drug information system of the statutory health insurance. Based on DDD, drug treatment rates were calculated per 100,000 people.

Results: From 2005 to 2016, the annual anticoagulant prescription rates per 100,000 persons increased by 135.8% (from 901.4 to 2125.9). By 2011, direct oral anticoagulants (DOAC) accounted for < 0.1% of all anticoagulants, but 49.9% in 2016. Over the same period, age-standardized hospital admissions for GIBs per 100,000 person-years decreased by 14% (from 128.89 to 110.87). Hospitalization rates for gastric ulcer and duodenal ulcer decreased steadily, and those for hematoma, melena and hematochezia continued to increase. Only the USGIH decreased from 2005 to 2011 (annual change of −3.35 (95% CI −5.44; −1.25) per 100,000 person-years) and subsequently increased (0.61, 95% CI −0,42; 1.65). Of all GIB cases, 5.8% received at least 6 red blood cell concentrates in 2005 and 4.6% in 2016. The two-phase time trend for USGIH was no longer present in this subgroup.

Conclusion: Our nationwide comparison of outpatient OAC treatment rates and hospitalization rates for GIBs showed that GIB hospitalization rates declined despite increasing OAC treatment rates from 2005 to 2016. With increasing impact of DOACs after 2011, this decline was not affected.

1. Introduction

Direct oral anticoagulants (DOAC) include a direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), which were developed and introduced into clinical practice almost 10 years ago [1–3]. They have replaced anticoagulation with vitamin K antagonists (VKA) in patients with atrial fibrillation (AF) [4,5] and venous thromboembolism (VTE) [6,7]. In Germany in 2016 around 80% of all DOACs were prescribed in patients with AF and 20% in patients with VTE [8].

A meta-analysis of randomized controlled phase III trials (RCTs) comparing anticoagulants in patients with AF found that the risk of intracerebral haemorrhage associated with DOACs is lower than that with VKA [9]. However, these meta-analyses also showed that treatment with DOACs could increase the risk of GI by 25% compared to VKAs [10–12]. Such meta-analyses from RCT to GIB could possibly be biased by survival distortions [13]. Because a large proportion of patients in these RCTs had pretreatment with VKA and a significant proportion of the included population had a low GIB risk during VKA. Meta-analyses cannot correct this bias if they are not performed at the

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patient level and consider only newly treated patients. Thus, the risk of bleeding in the real world could be even higher.

Accepting an increased risk of GIB associated with DOACs shift in treatment rates from VKA to DOAC would have had to impact GIB hospitalization rates in Germany in recent years, assuming that everything else remains the same. Therefore, we analyzed the nationwide time trends of prescribed anticoagulants in outpatients and evaluated their association with the GIB in Germany from 2005 to 2016.

2. Patients and methods

2.1. Nationwide hospitalization data

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 Remuneration 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 [14,15]. In brief, we identified all hospitalizations of the years 2005 through 2016 that included a primary diagnosis of GIB as listed in Table 1 by calendar year, sex, and 5-year age group. Gastric ulcer is coded as K25,*? and duodenal ulcer as K26,*?. In both codes the forth digit can be: “0” for acute with haemorrhage, “2” for acute with both, haemorrhage and perforation, “4” for chronic or unspecified with haemorrhage or “6” for chronic or unspecified with both, haemorrhage and perforation. Thus we included all these codes. Other GIB can be coded as hematochezia (K62.5), hematemesis (K92.0), melena (K92.1) and unspecific gastrointestinal haemorrhage (USGIH) (K92.2). In addition OPS-codes (operation and procedure key) for transfusion of red blood cell concentrate (RBC) in those patients are available.

2.1.1. Prescribed anticoagulants

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 defined daily doses (DDD) of all anticoagulants prescribed in these years 2005 to 2016 were provided by the WIDO (Wissenschaftliches Institut der AOK) which is a scientific institute of the statutory health insurance AOK in Germany.

The system of DDD was officially recommended by the World Health Organization as early as 1981 as a system for international drug consumption studies. DDD of a drug represents the mean daily maintenance dose (not initial dose or setting dose) for the main indication in an adult weighing 70 kg. It is a purely computational size, not necessarily the recommended dosage or the dose actually used Dosages of a drug.

2.2. Statistical methods

We calculated crude and age-standardized annual hospitalization rates for each kind of GIB per 100,000 persons. The German standard population 2011 was used for age standardization. In addition, we calculated annual drug treatment rates per 100,000 persons by using the following assumptions: a DDD of 365 reflects one patient continuously treated over one year. Thus 1000 DDDs of VKA correspond to 1000/365 = 2.7 patients taking VKAs over one year. As DDD data were not provided by age, we could only calculate crude drug treatment rates.

To estimate the absolute change of hospitalization rates for GIB, we used linear regression models with calendar year as the independent variable and the hospitalization per 100,000 as the dependent variable. With the exception of DOACs (market approval in 2008), we used the calendar years 2005 through 2016 for our modeling. We used SAS 9.4 (Cary, NC) for all analyses.

3. Results

Total numbers of all hospital admissions for GIBs, irrespective of whether or not they took anticoagulants, were 94,536 in 2005 and 97,251 in 2016 (+2.9%). Age-standardized rates per 100,000 person years decreased by 14% (from 128.89 to 110.97) (Supplementary Table 1). Age-standardized rates of gastric ulcer and duodenal ulcer steadily decreased and those of hematemesis and melena and steadily increased and that of hematochezia remained unchanged (Fig. 1). Only hospitalization rates for USGIH showed a biphasic curve. They decreased from 2005 to 2011 (annual change of −3.35 (95%CI −5.44; −1.25) per 100,000 person years) and increased subsequently (0.61, 95%CI −0.42; 1.65).

From all cases hospitalized for GIBs in 2005 32.8% received at least one transfusion of RBC. In 2016 the rate was 34.0%. In this subgroup, bleeding rates associated with gastric and duodenal ulcer increased from 2005 to 2008 and decreased afterwards. Unspecified GIBs still showed a biphasic curve (Fig. 2).

Table 1
Drug treatment rates (treated persons per 100,000 person years) in 2005–2016. Regression coefficients ß with 95% confidence intervals (CI) from linear regression models with year as independent and drug treatment rate as dependent variable.

Drug	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	ß (95% CI)
All vitamin K antagonists	901.4	963.0	1025.5	1096.9	1156.0	1205.2	1274.1	1301.5	1261.6	1231.5	1159.4	1065.9	2005–2011: 61.9 (59.2; 64.6) 2012–2016: −57.3 (−81.8; −32.9)
All DOACs	0	0	0	0.1	0.7	1.6	10.3	135.5	391.3	655.4	845.7	1060.0	2012–2016: 230.3 (202.8; 257.9)
All vitamin K antagonists + all DOACs	901.4	963.0	1025.5	1097.0	1156.6	1206.8	1284.4	1437.0	1652.9	1886.9	2005.1	2125.9	2005–2011: 63.1 (60.3; 66.0) 2012–2016: 173.0 (122.2; 223.8)
All heparines + Fondaparinux	219.6	240.8	280.2	331.0	376.5	424.2	473.2	493.2	480.6	491.7	492.3	464.2	2005–2011: 43.7 (38.9; 48.5) 2012–2016: −4.6 (−16.3; 7.0)

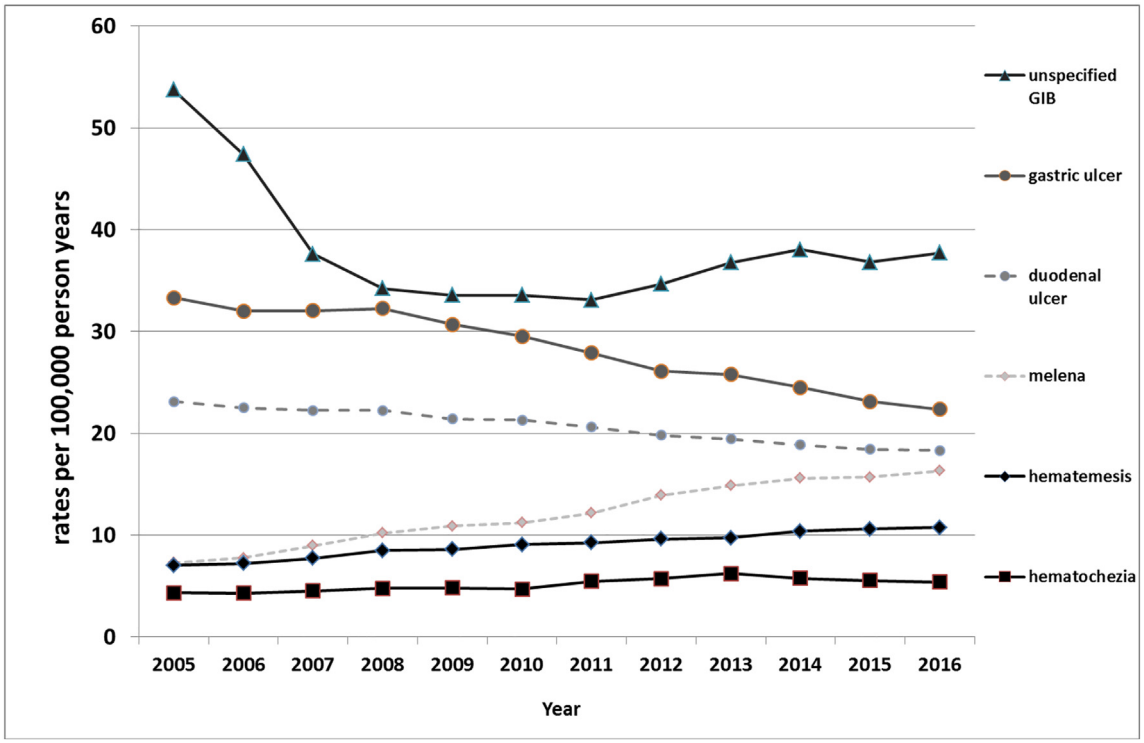

Fig. 1. Age-standardized hospitalization rates (per 100,000 person years) for all cases hospitalized with different types of GIBs in Germany, 2005–2016.

From all cases hospitalized for GIBs in 2005 5.8% received at least 6 RBCs in 2005 and 4.6% in 2016. In this subgroup, bleedings rate associated with gastric and duodenal ulcer still increased from 2005 to 2008 and decreased thereafter, but unspecified GIBs showed a decreasing trend from 2005 to 2016 (Fig. 3).

3.1. Anticoagulants

From 2005 to 2016, annual OAC treatment rates per 100,000 person years increased by 135.8% (from 901.4 to 2125.9). The annual VKA treatment rate per 100,000 person years increased from 2005 to 2011 (from 901.4 to 1274.1, annual rate change 61.9 per 100,000 person years, 95%CI 59.2; 64.6) and decreased from 2012 to 2016 (from

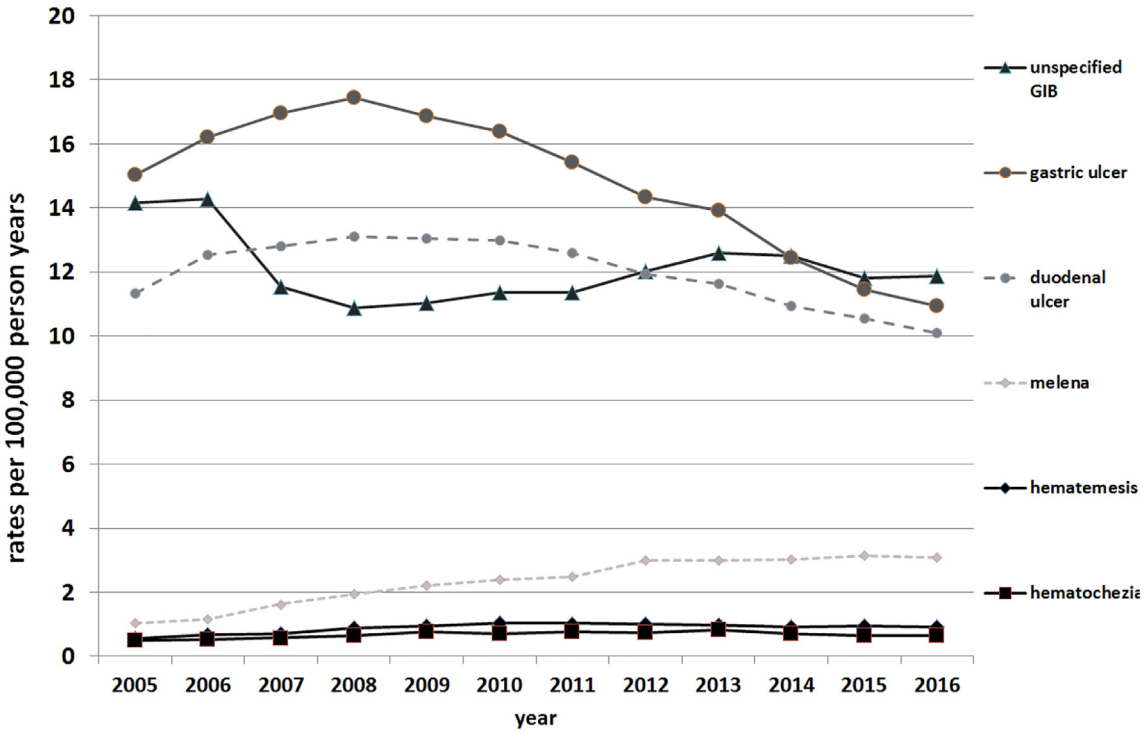

Fig. 2. Age-standardized hospitalization rates (per 100,000 person years) for all cases hospitalized with different types of GIBs that had required at least 1 RBC in Germany, 2005–2016.

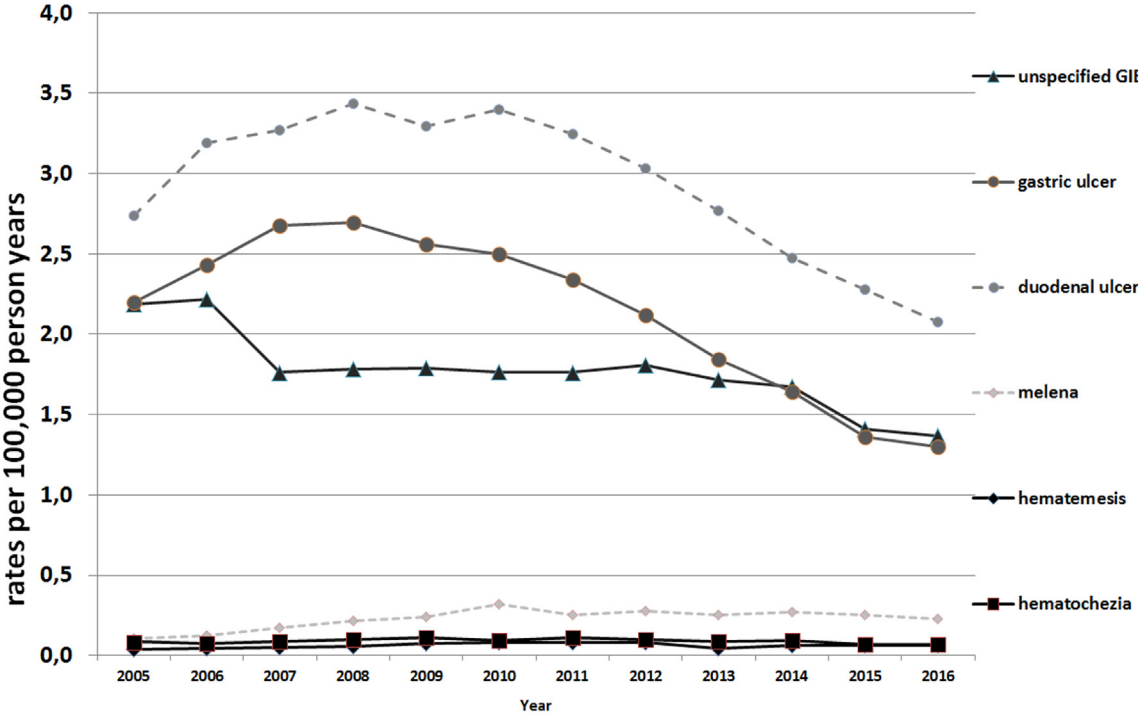

Fig. 3. Age-standardized hospitalization rates (per 100,000 person years) for all cases hospitalized with different types of GIBs that had received at least 6 RBCs in Germany, 2005–2016.

1301.5 to 1065.9, annual rate change −57.3 per 100,000 person years, 95%CI −81.8; −32.9). DOACs became available in 2008 for the first time and within the short period of 8 years the annual DOAC treatment rates per 100,000 person years increased from 0.1 in 2008 to 1060.0 in 2016 (annual rate change +230.3 per 100,000 person years, 95%CI 202.8; 257.9).

4. Discussion

The presented data show an increase in the prescription of OAC in outpatients since 2005 as well as a 14.0% decrease in age-adjusted hospitalization rates for GIB in Germany. An increase in hospitalization rates associated with the increase in prescription rates of DOACs from 2011 was not observed. Looking more closely at the various subtypes of GIBs, bleeding associated with gastric and duodenal ulcer, as well as hematochezia, hematemesis, and melena-coded bleeding, show linear trends over the period 2005 to 2016, unaffected by the introduction of DOACs. Only GIBs coded as USGIH showed a two-phase trend with a small increase from 2011, the year in which a significant number of DOACs were prescribed.

Although we do not know how hospitalization rates would have changed without the introduction of DOACs in Germany, there is some evidence from the literature that the number of GIBs remained unchanged or decreased in the last decades. Most data are available only for upper gastrointestinal haemorrhage (UGIH). A longitudinal study of UGIH hospitalizations by using the Nationwide Inpatient Sample from 1989 to 2009 reported a decrease from 4.5% in 1989 to 2.1% in 2009 non-variceal UGIH mortality rate [17]. A retrospective, observational cohort study of the Nationwide Inpatient Sample from 2002 to 2012 investigated trends in etiology of UGIH in hospitalized patients in the USA. The hospitalization rate of UGIH in the USA decreased by 21% from 2002 to 2012 from 81 to 67 cases per 100,000 population. The greatest declines occurred for gastritis and peptic ulcer disease, which decreased by 55 and 30%, respectively. There were increases in bleedings associated with neoplasm, Dieulafoy lesions, angiodysplasia, and esophagitis, which increased by 50, 33, 32 and 20%, respectively [16]. Another study provided data from the Scottish Morbidity Records database on inpatient and day-case hospital discharges from non-obstetric and non-psychiatric hospitals in Scotland. There was no significant change in annual number of admissions for UGIH over time during January 2000 and October 2009 [18]. All in all hospitalization rates of GIB depend on the incidence of specific diseases and population trends in use of treatments for peptic ulcer disease, improved hemostatic techniques, and overall care. As the rate of GIBs is influenced by various parameters use of OAC is only one aspect in this spectrum. A general spread in PPI-therapy might be the most important reason for a decreasing rate of UGIH. A more aggressive endoscopic treatment might **improve** outcome of bleedings and the use of anticoagulants might increase the role of bleeding rates that are not associated with peptic ulcers such as neoplasm, Dieulafoy lesions, angiodysplasia and esophagitis.

The role of DOACs for GIB is was analyzed in different meta-analysis. One from 2013 based on 43 randomized controlled trials reported an overall OR for clinically relevant bleeding in patients taking DOACs of 1.16 (95% CI, 1.00_1.34). Among the drugs studied, the OR for apixaban was 1.23 (95% CI, 0.56_2.73), the OR for dabigatran was 1.58 (95% CI, 1.29_1.93), the OR for edoxaban was 0.31 (95% CI, 0.01_7.69), and the OR for rivaroxaban was 1.48 (95% CI, 1.21_1.82) [19]. Another one from 2016 based on eight cohort studies reported pooled incidence rates of GIB of 4.50 [95%confidence interval (CI) 3.17, 5.84] and 7.18 (95% CI 2.42, 12.0) per 100 patient-years among dabigatran and rivaroxaban users, respectively. The summary risk ratio (RR) was 1.21 (95% CI 1.05, 1.39) for dabigatran compared with warfarin, and 1.09 (95% CI 0.92, 1.30) for rivaroxaban [20].

In line with current US literature [16,17], our analysis shows a decline in annual hospitalization rates for GIBs in Germany, although prescriptive rates for all anticoagulants have increased. This finding is independent of the introduction of the DOACs with a potentially higher risk for GIBs in 2011. Even before 2011, VKA prescriptions increased by 34% compared to 2005 and this was not associated with an increase in GIBs. Thus, OAC treatment seems to have become generally safer regarding GIBs during this period. The **later** shift towards **DAOC** has had

no influence on this effect. In detail, the hospitalization rates of gastric and duodenal bleeding decreased steadily over time. In contrast to this development, we noted a small but steady increase in rates of hospitalization for hematochezia, hematemesis and melena. **Comparable data of these bleeding types are scarce** [21]. A two phase curve is only visible for USGIH. In 2005, there was a high USGIH rate, which declined by 38% until 2011 and then increased slightly by 13% until 2016. The reason for this trend is unknown in particular for the decrease until 2011. The increase thereafter corresponds to the nationwide inpatient randomized retrospective observational cohort study which found an increase in neoplasia-related bleeding, lesions of Dieulafoy, angiodysplasia and esophagitis in the period from 2002 to 2012 [16]. Another study by Desai et al. reported that the rate of lower GIBs appears to be increased in DOACs-treated patients compared to VKAs, but they did not explain the exact mechanisms [22]. Severe GIBs requiring six or more RBC decreased within in this period from 5.8% to 4.6% in 2016. There may be various explanations for these generally decreasing rates of transfusion. Patients who take anticoagulants have a higher awareness of bleeding. For example, a group from Japan reports that the incidence of Forrest Ia bleeding in the antithrombotic group was lower ($p < 0.001$) [23]. On the other hand, the more aggressive and effective endoscopic treatment of GIBs in recent years has reduced the need for RBCs as well as more restrictive adult transfusion guidelines with acute upper GIB [24].

5. Strengths 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 factors that limit our results. First, our ecological study design did not allow for confusion, including indications for treatment, treatment quality, polypharmacy and relevant comorbidities. Second, it should be noted that the DDD does not reflect the recommended or actually prescribed daily dose, but represents a technical measurement and comparison unit. Compared with other parameters such as the number of packages delivered or the resulting sales DDD has the advantage that the consumption of a drug is measured directly on the basis of a previously defined amount of active ingredient. The advantage of the DDD as a comparison measure is also that changes in the pack sizes or dosages cannot distort the measured consumption. On the other hand, VKA is administered in a flexible dosage (one package may take 30 or 90 days), depending on the very individual dosage requirements, to achieve the desired INR. DOACs are administered once or twice daily according to a fixed schedule. The calculated DDD, which reflects a patient treated continuously for over a year, is a theoretical assumption with a significantly greater problem for VKAs than for DOACs. Third, we have relied on the coded primary diagnoses contained in the national hospital file, and there are no systematic studies on the quality of coding. However, it is reasonable to assume non-differential coding errors, that is, the miscoding of the primary diagnosis has nothing to do with the history of VKA or DOAC recording. Fourth, GIBs may occur shortly after OAC treatment begins. Due to short-term treatments, the estimated number of patients receiving OAC could be even higher. Finally, it should be noted that the analysis is based on individual cases and not on individual patients. As a result, a patient could be included in the statistics multiple times if he or she had a GIB at two different times within a year.

In conclusion, our nationwide comparison of outpatient OAC treatment rates and hospitalization rates for GIBs showed that GIB hospitalization rates declined despite increasing OAC treatment rates from 2005 to 2016. With increasing impact of DOACs after 2011, this decline was not affected. Since our analysis is only descriptive, we cannot prove the causality of observation.

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Contributions of the authors

Jan-Erik Guelker: acquisition of data; analysis and interpretation of data; finalization of the manuscript

Dimitrios Ilousis: analysis and interpretation of data; drafting of the manuscript

Knut Kröger: important intellectual content; critical revision of the manuscript; study supervision

Frans Santosa: critical revision of the manuscript;

Bernd Kowall: acquisition of data; statistical analysis; technical support

Andreas Stang: critical revision of the manuscript; study supervision

Declaration of Competing Interest

JE. Guelker, D. Ilousis, F. Santosa, B. Kowall and A. Stang do not have any conflicts of interest.

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