Increasing Use of Anticoagulants in Germany and Its Impact on Hospitalization for Tooth Extraction

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Abstract

Objectives   This article aimed to compare nationwide time trends of oral anticoagulant prescriptions with the time trend of hospitalization for tooth extraction (TE) in Germany from 2006 through 2017.

Patients and Methods   We derived the annual number of hospital admissions for TE from the Nationwide Hospital Referral File of the Federal Bureau of Statistics and defined daily doses (DDD) of prescribed anticoagulants in outpatients from reports of the drug information system of the statutory health insurance.

Results   From 2005 to 2017, annual oral anticoagulation (OAC) treatment rates increased by 143.7%. In 2017, direct oral anticoagulants (DOACs) represented 57.1% of all OAC treatments. The number of cases hospitalized for TE increased by 28.0 only. From all the cases hospitalized for TE in Germany in 2006, 14.2% had a documented *history of long-term use of OACs.* This proportion increased to 19.6% in 2017. Age-standardized hospitalization rates for all TE cases with *long-term use of OACs* increased from 6.6 in 2006 to 10.5 cases per 100,000 person-years in 2014 and remained almost unchanged thereafter.

Conclusion   Our comparison showed that the large increase in OAC treatment rates in general from 2006 to 2017 had only a small impact on hospitalized TE cases with long-term use of OAC which flattens since 2014.

Keywords
► tooth extraction
► vitamin K antagonists
► direct oral anticoagulants
► bleedings

Introduction

Bleeding after tooth extraction (TE) ranges from minor bleeding to life-threating hemorrhagic shocks and is one of the main complications in patients on oral anticoagulation (OAC) with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKA).[1–3] DOACs include a direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivarox-aban, apixaban, and edoxaban), which were developed and introduced into clinical practice almost 10 years ago.[4–6] They have largely replaced anticoagulation with VKA in patients with atrial fibrillation (AF)[7,8] and venous thromboembolism.[9,10] In Germany, around 80% of all DOACs were prescribed in patients with AF and 20% in patients with venous thromboembolism in 2016.[11] In 2015 in the United Kingdom,

17.6% of all people with type 2 diabetes mellitus who had OACs received DOACs.[12]

A recent study from Switzerland with 64 patients with bleeding from TE showed that delayed bleeding occurred more frequently in anticoagulated patients with both DOAC and phenprocoumon than in patients without anticoagulation.[1] Bleeding events in anticoagulated patients with DOAC and phenprocoumon equally require longer emergency department treatment and more frequent surgery. Another study from Italy that enrolled 130 patients reported that DOAC and VKA patients had the same incidence of bleeding complications after simple single TE. Bleeding events were not statistically significant and not clinically relevant.[13]

In contrast to these studies with small patient numbers, we analyzed the nationwide time trends of prescribed anticoagulants in outpatients and assessed their association with hospital stays for TE and bleeding in Germany from 2006 to 2017. If VKAs and DOACs have the same risk of bleeding, the introduction of DOACs should have no impact on hospital admission rates for TE.

Patients and Methods

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 the National Classification of Operations and Procedures—to the Institute for the Hospital Remuneration System (InEK). After a plausibility control, the InEK forwards the 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 2006 through 2017 that included a procedure code as *tooth extraction* (TE) (OPS code [operation and procedure code] 5–230) by calendar year, sex, and 5-year age group. These were separated for subcodes coded at digit 5 as $0 =$ one root tooth, $1 =$ multiple root tooth, $2 =$ multiple teeth in one quadrant, $3 =$ multiple teeth in different quadrants, $4 =$ multiple teeth in both jaws, $5 =$ all teeth, x = others, and y = not specified. Among these cases, we looked for those with the additional diagnosis *personal history of long-term (current) use of anticoagulants* (ICD code Z92.1). In those with an OPS code 5–230 and ICD code Z92.1, we looked for those with the OPS code (8–800 = 1–5 red blood cell [RBC] concentrates, 8–800.1 = more than 5 RBCs) for transfusion of RBCs. In summary, only patients were considered for whom the TE was performed under inpatient conditions and not those who were hospitalized due to a bleeding complication as a result of an outpatient TE. Only severe bleeding that required a blood transfusion could be taken into account, as it was documented in the DRG system for reimbursement.

Bleeding complications due to TE that do not require a blood transfusion are not systematically documented in the DRG system.

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 SHI funds which, being public-law corporations, are financially and organizationally independent.

The SHI provides regular reports of the SHI-Drug Information System according to the German law regulation (§ 302 SGB V). These reports are based on billing data from all SHI companies in Germany. For data confidentiality, all data are anonymized. Detailed lists of defined daily doses (DDD) of all anticoagulants prescribed in the years 2005 to 2016 were provided by the WIDO (Wissenschaftliches Institut der AOK) which is a scientific institute of the SHI AOK in Germany.

Drug consumption can be expressed in cost, number of units, number of prescriptions, or by the physical quantity of drugs. However, these variables can vary between regions and countries over time. This limits comparisons of drug consumption at an international level. To address this, a technical unit of measurement, the DDD, was created. 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. The DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose (PDD). Therapeutic doses for individual patients and patient groups will often differ from the DDD as they will be based on individual characteristics such as age, weight, ethnic differences, type and severity of disease, and pharmacokinetic considerations. Drug utilization data presented in DDDs give a rough estimate of consumption and not an exact picture of actual use. DDDs provide a fixed unit of measurement independent of price, currencies, package size, and strength enabling the researcher to assess trends in drug utilization and to perform comparisons between population groups.

Statistical Methods

We calculated crude and age-standardized annual hospitalization rates for each kind of TE 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 1 year. Thus, 1,000 DDDs of VKA correspond to 1,000/365 = 2.7 patients taking VKAs over 1 year. As DDD data were not provided by age, we could only calculate crude drug treatment rates. We used SAS version 9.4 (Cary, North Carolina, United States) for all analyses. We have already published similar analyses for gastrointestinal and urogenital bleedings.[16,17]

Ethics

According to the occupational regulations for the North Rhine-Westphalian physicians, retrospective epidemiological research

projects are specifically excluded from the necessity of an ethics vote. Specific linking of cases and procedures is possible but not allowed for legal reasons. Thus, institutional review board approval and patients' informed consent are not necessary.

Results

Anticoagulants

From 2005 to 2017, annual OAC treatment rates per 100,000 person-years increased by 143.7% (from 901.4 to 2,196.3). The annual VKA treatment rate increased from 2005 to 2011 (from 901.4 to 1,274.1 persons taking a DDD daily per 100,000 person-years) and decreased from 2012 to 2017 (from 1,301.5 to 943.0; ►Table 1). Even annual treatment rate of nonoral anticoagulants (heparin and fondaparinux) decreased from 2013 to 2017. DOACs became available in 2008 for the first time and within the period of 9 years, the annual DOAC treatment rates per 100,000 person-years increased from 0.1 in 2008 to 1,253.3 in 2017. In 2017, DOACs represented 57.1% of all OAC treatments.

Hospitalization Rates

Total number of all hospital admissions in Germany was 16,229,172 cases in 2006 and increased by 16.5% to 18,900,149 cases in 2017. Cases of aged 65 years and older increased by 25.2%. From all cases hospitalized in Germany in 2006, 3.6% had a documented code ICD Z92.1, indicating a *personal history of long-term (current) use of anticoagulants.* This rate increased to 9.6% in 2017. In cases of aged 65 years and older, the figures were 6.7% in 2006 and 17.8% in 2017.

The number of hospitalization with a documented code indicating the procedure of TE was 35,524 in 2006 and increased by 28.0% to 45,475 in 2017 ►Table 2. Cases of aged 65 years and older increased by 58.5%. From all the cases hospitalized for TE in Germany in 2006, 14.2% had a documented *history of long-term use of anticoagulants.* This rate increased to 19.6% in 2017. In cases of aged 65 years and older, the figures were 29.4% in 2006 and 36.6% in 2017.

Documented transfusions of RBCs were rare in general. Up to three cases were documented in single years only. ►Table 3 shows age-standardized hospitalization rates (per 100,000 person-years) for all cases hospitalized for TE (5–230.*) and those for TE with an additional code indicating chronic

treatment with anticoagulation (5–230.* + Z92.1). Age-standardized rates for all cases hospitalized for TE increased from 2006 to 2012 by 10.2 cases and remained almost unchanged thereafter. The rate of those cases with OAC rose from 6.6 to 10.5 cases per 100,000 person-years from 2006 to 2014 and remained almost unchanged thereafter (►Fig. 1).

Discussion

The presented data show an increase in age-standardized hospitalization rates for TE from 2006 to 2014 in Germany but not afterward. At the same time, the number of cases with chronic anticoagulant use in these cases did not increase after 2014 either. Relevant bleeding in these cases, which required RBC transfusion, was rare.

Bleeding events are one of the most important complications after TE, These bleedings range from frequent minor bleeding to rare life-threating hemorrhagic shock, even in healthy patients.[18] Previous studies found no significant difference in bleeding incidence between patients on oral anticoagulant therapy with the VKA warfarin than with patients without anticoagulant medication.[19,20] In analogy to VKAs, guidelines on the management of anticoagulants and TE therefore recommend continuing DOAC in most dental interventions.[21] Most bleeding events from TE with anticoagulation can be stopped within the outpatient setting. However, serious bleeding complications can lead to admission to the emergency department. This is becoming more common with the increasing use of DOACs.[1] While treatment guidelines exist for the perioperative management of rivaroxaban, a recent literature review of DOACs and TE found limited evidence on the effects of DOACs on postextraction bleeding. A lack of evidence-based work on the management of bleeding events has been identified.[20] A recent literature review about DOACs and their implications in dentistry suggests that these drugs are relatively safe in terms of general and perioperative bleeding.[2,3] It is of paramount importance to individualize the approach and assess the difficulty of the procedure, the risk of bleeding, the risk of embolism, and the renal function of each specific patient. Bridging with heparin, often used in patients on VKAs, is never recommended in patients with DOACs. Only the suspension or the delay of a single dose can be taken into account. A nonstop protocol for low bleeding risk in

Table 1 Drug treatment rates in 2005–2017

Drug	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
All VKAs	901	963	1,025	1,096	1,156	1,205	1274	1,301	1,261	1,231	1,159	1,065	943
All DOACs	0	0	0	0.1	0.7	1.6	10.3	135.5	391.3	655.4	845.7	1,060.0	1,253.3
All VKAs + all DOACs	901	963	1,025	1,097	1,156	1,206	1,284	1,437	1,652	1,886	2,005	2,125	2,196
All heparins + fondaparinux	219	240	280	331	376	424	473	493	480	491	492	464	443

Abbreviations: DOACs, direct oral anticoagulant; VKAs, vitamin K antagonists.
Note: Estimated are treated persons per 100,000 person-years accepting that one defined daily dose represents one person and 1 day.

Table 2 Absolute numbers of hospitalized cases with an OPS-code covering tooth extraction (5–230.*), within these cases those with an additional OPS-code indicating chronic treatment with anticoagulation (Z92.1) and those who had received transfusion of erythrocyte concentrate (OPS-code 8–800.0 + 8–800.1) for representative years in the period from 2006 to 2017

	2006	2009	2012	2015	2017	Delta in %
All cases	16,229,172	17,190,603	17,975,002	18,664,953	18,900,149	16.5
With anticoagulation (Z92.1)	581,406	850,152	1,102,889	1,519,246	1,805,169	210.5
≥ 65 years	6,892,570	7,645,253	8,022,459	8,428,180	8,627,311	25.2
With anticoagulation (Z92.1)	463,136	70,0270	923,887	1,285,104	1,536,649	231.8
All cases with tooth extraction						
5–23	35,524	39,630	44,703	45,780	45,475	28.0
5–230	19,015	20,005	22,915	24,241	24,855	30.7
5–231	17,493	20,681	22,996	22,973	22,092	26.3
5–232	1,472	1,615	1,700	1,673	1,581	7.4
5–233	367	225	281	207	211	−42.5
5–235	1,283	1,409	1,345	1,276	1,251	−2.5
5–236	7	10	7	14	11	57.1
5–237	1,794	1,796	1,839	1,643	1,341	−25.3
With anticoagulation (Z92.1)	5,050	6,518	7,684	8,698	8,918	76.6
With transfusion (8–800.0 + 8–800.1)	1	2	1	1	1	
All cases ≥ 65 years with tooth extraction						
5–23	11,629	14,357	17,056	18,155	18,433	58.5
5–230	6,893	7,722	9,175	9,966	10,468	51.9
5–231	5,716	7,685	9,104	9,486	9,168	60.4
5–232	105	107	173	157	143	36.2
5–233	147	91	112	81	87	−40.8
5–235	280	408	398	397	449	60.4
5–236	4	6	4	8	6	50.0
5–237	317	368	363	307	272	−14.2
With anticoagulation (Z92.1)	3,420	4,540	5,575	6,501	6,740	97.1
With transfusion (8–800.0 + 8–800.1)	0	2	0	1	0	

Note: Table includes figures for all patients and those cases ≥ 65 years only.

dentoalveolar surgery is published.[22] Two recently published studies looked at protocols for stopping and not interrupting in dentoalveolar surgical procedures and reported no difference in bleeding events between the two approaches.[23,24]

In line with the literature, our analysis shows that the rate of patients with a personal history of long-term use of OAC in Germany rose steadily from 2006 to 2017. The rate in people 65 years and older is even higher and shows a larger increases than in others, as this age is especially mentioned in the CHADS$_2$VASC$_2$ score, which recommends prophylactic OAC in patients with AF.[7] People hospitalized for TE have a higher rate of OAC than the average of all cases in hospital. This could indicate that OAC could be a reason for hospitalization in case of TE. Unfortunately, we cannot prove that. In addition to the literature, our analysis shows that although the rate of patients with a personal history of long-term use of OAC in Germany steadily increased from 2006 to 2017, the number of cases hospitalized for TE increased only until 2014

and has remained rather constant thereafter. This finding correlates with the introduction of the DOACs. Although they were introduced primarily in 2008, clinical important prescription rates were achieved in 2012. Therefore, the introduction of the DOACs and the switch to DOACs as the first-line therapy in patients with AF appears to have an impact on TE hospitalization rates. OAC treatment with DOACs appears to have been generally safer or easier to manage with respect to TE. Relevant bleeding that required RBC transfusion was a rare finding during the period from 2006 and 2017. Only single cases were documented and a specific analysis was not possible. Unfortunately, we do not have data about bleeding complications that do not require a blood transfusion or other complications such as necessity of second intervention associated with OAC.

It is important to note that we report only about patients who have been hospitalized for TE. Our analysis does not include patients with TE on an outpatient basis who were

Table 3 Crude rates and age-standardized hospitalization rates (per 100,000 person-years) for all cases hospitalized for tooth extraction (5–230.*) and those for tooth extraction with an additional code indicating chronic treatment with anticoagulation (5–230.* + Z92.1) in Germany, 2006–2017

| Year	Crude rates		Age-standardized rates[a]	
	Tooth extraction	Tooth extraction + anticoagulation	Tooth extraction	Tooth extraction + anticoagulation
2006	43.1 (0.23)	6.1 (0.09)	44.2 (0.24)	6.6 (0.09)
2007	45.0 (0.23)	7.0 (0.09)	45.9 (0.24)	7.4 (0.10)
2008	46.2 (0.24)	7.3 (0.09)	47.0 (0.24)	7.6 (0.10)
2009	48.4 (0.24)	8.0 (0.10)	49.0 (0.25)	8.2 (0.10)
2010	50.4 (0.25)	7.8 (0.10)	50.7 (0.25)	7.9 (0.10)
2011	51.9 (0.25)	8.5 (0.10)	52.0 (0.25)	8.5 (0.10)
2012	54.6 (0.26)	9.4 (0.10)	54.4 (0.26)	9.3 (0.11)
2013	55.7 (0.26)	10.2 (0.11)	55.2 (0.26)	10.0 (0.11)
2014	56.9 (0.27)	10.9 (0.12)	56.1 (0.26)	10.5 (0.11)
2015	56.0 (0.26)	10.6 (0.11)	55.1 (0.26)	10.2 (0.11)
2016	56.5 (0.26)	10.9 (0.11)	55.4 (0.26)	10.4 (0.11)
2017	55.0 (0.26)	10.8 (0.11)	53.7 (0.26)	10.1 (0.11)

Note: Standard errors are shown in brackets.
[a]The German Standard Population 2011 was used for age standardization of the rates.

sent to an emergency room for severe bleeding as a complication and who were hospitalized finally.

Strengths and Limitations

A major strength of this study is the large dataset, which includes virtually all German hospitals and the observation period of 11 years. This allows a unique view at the current clinical practice. Moreover, to the best of our knowledge,
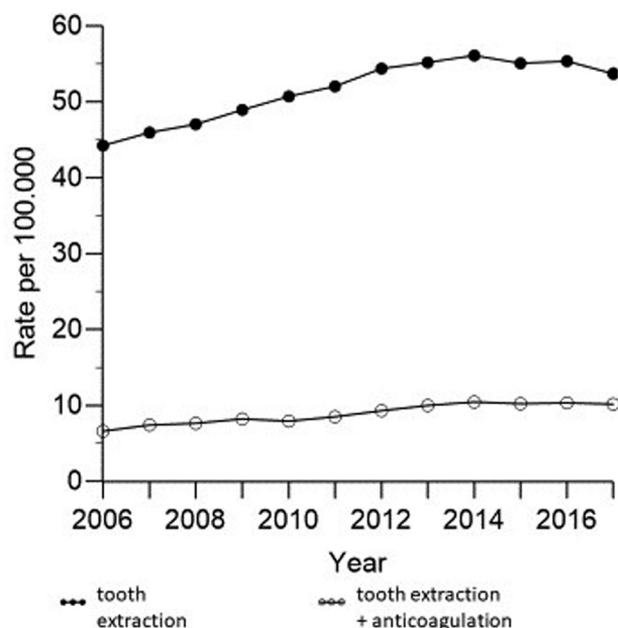
Fig. 1 Age-standardized hospitalization rates (per 100,000 person-years) for all cases hospitalized for tooth extraction (5–230.*) and those for tooth extraction with an additional code indicating chronic treatment with anticoagulation (5–230.* + Z92.1) in Germany, 2006–2017.

there is currently no other publication that deals with topic from a population-based viewpoint in Germany.

There are factors that limit our results. First, we studied TE only in hospital patients. The majority of TE is performed on an outpatient basis and decreased from 13.243 Mio operations in 2006 to 12.605 Mio in 2017 in Germany, as shown on the homepage of the German Federal States Dental Chamber (https://www.kzbv.de/jahrbuch-2020.768.de.html). In contrast to this overall downward trend, number of TE hospital admission increased. Second, our ecological study design did not allow to analyze the effect of confounding, including indications for treatment, treatment quality, polypharmacy, and relevant comorbidities. However, OAC could be one aspect that is triggering an increasing number of hospital admissions for TE. Third, it should be noted that the DDD does not reflect the recommended or actually PDD, 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. A further advantage of the DDD as a comparison measure is 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 who was treated continuously for over a year, is a theoretical assumption with a significantly greater problem for VKAs than for DOACs. Fourth, we have no information about periprocedural management of OAC. VKA could have been bridged or both VKAs and DOACs could have been continued or discontinued perioperatively. Fifth, improvements in surgical

techniques and tools may possibly have an influence on reduced hospitalizations for a TE and bleeding complications. Sixth, we have relied on the coded procedure (TE) and coding of long-term use of OACs among secondary diagnoses contained in the national hospital file, and there are no systematic studies on the quality of coding. Seventh, 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 TE at two different times within a year.

Finally, it has to be mentioned that our analysis is based on hospital cases. The majority of TEs is done on an outpatient basis. It can be assumed that only those patients with risk factors or more complex procedure of TE are sent to a hospital.

In conclusion, our nationwide comparison of outpatient OAC treatment rates and hospitalization rates for TEs showed that the large increase in OAC treatment rates in general from 2006 to 2017 had only little impact on TE cases in hospital with long-term use of OAC which flattens since 2014. Since our analysis is only descriptive, we cannot prove the causality of the observation.

Conflict of Interest
The authors declare that they have no conflict of interest.

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