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Oral Anticoagulation and Mortality in Cases with Intracranial Bleeding: Analysis of Nationwide Prescription and Hospitalization Data

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Abstract

Objectives To demonstrate the safety of direct oral anticoagulants in relation to intracranial bleeding (ICB), we compared the number of patients taking anticoagulants in all cases of hospitalization and cases of hospitalization for ICB over time in Germany. We analyzed the intrahospital mortality of ICB cases in relation to long-term use of anticoagulants (LUAs).

We performed a retrospective registry analysis of nationwide German hospitalizations including all hospital admissions and admission for ICB in patients aged ≥60 years in the period from 2006 to 2020 and separated for LUAs.

Results In 2006, the age-standardized rate of hospitalized male patients with LUAs was 7.3% and that of female patients was 5.6%. In 2020, the rates increased to 22.0 and 17.7% for male and female patients, respectively. Among patients hospitalized for ICB in 2006, 7.0 and 5.6% were male and female patients with LUAs, respectively. In 2020, the rate increased to 13.7% for males and 10.8% for females.

In 2006, age-standardized mortality rates of male and female patients with ICB without LUAs were 24.1 and 23.9%, respectively. In 2020, the rate slightly decreased to 22.7% in males, but it remained almost unchanged in females at 23.8%. In the cases with LUA, the mortality rate decreased from 30.1 to 24.3% in males and from 28.4 to 24.2% in females in the same period.

Conclusion LUA seems to be safe because there is a slower increase of the rate of LUAs in ICB cases than in generally hospitalized cases in the period from 2006 to 2020. In addition, mortality in ICB cases with LUA tends to decrease compared to cases without LUA.

Keywords

- intracerebral bleeding
- vitamin K antagonists
- direct oral anticoagulants
- hospitalization
- mortality

Introduction

Intracranial bleedings (ICBs) occur as a consequence of craniocerebral trauma or without external influence in 20% of strokes, in coagulation disorders, or disorders of blood vessels (aneurysms, arteriovenous malformation).[1]

Direct oral anticoagulants (DOACs) entered the market in 2008 and have become widely used since 2010. Their

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advantages over vitamin K antagonists (VKA) in terms of practicability and bleeding rates increased their acceptance.[2] A meta-analysis on the risk of ICB among DOACs or VKAs in patients aged ≥75 years described a significantly reduced risk for DOACs with a hazard ratio (HR) of 0.58 (95% confidence interval [95% CI]: 0.50–0.67).[3] A meta-analysis of 19 trials comparing hematoma volume, hematoma expansion, and mortality in VKA-ICB versus non-anticoagulation-associated ICB established a more unfavorable course of all these parameters in VKA-ICB patients.[4] A recent study including 193 ICB patients showed significantly smaller hematoma volumes under DOACs in comparison to VKAs and a significantly lower 30-day intrahospital mortality rate of DOAC-ICB, even before the introduction of specific antidotes.[5]

DOACs might have affected the ICB rate in Germany by different aspects. The prescription rates of DOACs have increased dramatically over the last decade in Germany,[6] which could have led to more ICB cases. The lower bleeding risk of DOACs might have compensated for such an increase. If DOACs cause smaller intracranial bleeding generally, overall mortality in ICB cases should have decreased.

To look for these effects in the German population, we compared the nationwide time trends of general hospitalization and hospitalization for ICB with and without long-term use of anticoagulants (LUAs) in Germany and finally intrahospital mortality of ICBs dependent on LUAs.

Patients and Methods

This is a retrospective cohort study including the nationwide hospitalization data documented in the Diagnosis-Related Groups Statistic (DRG). The nationwide hospitalization data documented in the DRG represent an annual survey of all hospital cases in Germany that were accounted for by case rates. All the 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. The principles of the analysis of this hospitalization file have been published several times previously.[7,8]

In brief, we asked the Federal Bureau of Statistics to identify all hospitalizations in the period from 2006 to 2020 that have a principal diagnosis of ICB (I60: subarachnoid bleeding and I61: intracerebral bleeding) by calendar year, sex, and 5-year age groups. Among these cases, we looked for those with LUAs, defined as the additional diagnosis of "personal history of long-term (current) use of anticoagulants" (ICD code Z92.1). Finally, we received a defined data set from the Federal Bureau of Statistics including this information from all fully reimbursed inpatient cases. For this analysis, we included all the patients aged ≥60 years.

The primary outcome was intrahospital mortality documented in the DRG. According to the occupational regulations for the North Rhine-Westphalian physicians, retrospective epidemiological research projects are specifically excluded from the requirement of an ethical approval. Specific linking of cases and procedures is possible but not allowed for legal reasons. Thus, institutional review board approval and patients' informed consent were not necessary for this study.

For all hospitalized patients without I60/I61, we calculated the age-standardized proportions of patients with anticoagulation for 2006 to 2020 separately for men and women —hospitalized patients from 2006 were used as reference population for the age standardization. The same was done for patients with I60/I61—here all patients with I60/I61 from 2006 were used as the reference population.

For patients with I60/I61, sex-specific age-standardized mortality was calculated for 2006 to 2020 separately for patients with and without anticoagulation—all the patients with I60/I61 from 2006 were used as the reference population. Calculations were done using SAS version 9.4 (SAS Institute, Cary, United States).

Results

Long-Term Use of Anticoagulants

In 2006, a total of 8,026,468 patients were hospitalized. The age-standardized rate of male patients with LUAs was 7.3% (95%CI: 7.3–7.3) and that of female patients was 5.6% (95% CI: 5.6–5.6; ►Table 1, ►Fig. 1). In 2020, hospitalized cases increased to 8,921,978 and the rate of males with LUAs increased to 22.0% (95% CI: 21.9–22.0) and that of females to 17.7% (95% CI: 17.6–17.7). Among all cases hospitalized for ICB in 2006 ($n = 30,792$), the rate of males with LUAs was 7.0% (95% CI: 6.5–7.4) and that of females with LUAs was 5.6% (95% CI: 5.3–6.0). In 2020, cases with ICB sum up to 31,650. The rates of males and females with LUA increased to 13.7% (95% CI: 13.1–14.3) and 10.8% (95% CI: 10.3–11.3), respectively.

Mortality of ICB Cases

In 2006, the age-standardized mortality rates in all ICB cases without LUAs in males and females were 24.1% (95% CI: 23.2–25.0) and 23.9% (95% CI: 23.1–24.6), respectively. In 2020, these mortality rates slightly decreased to 22.7% (95% CI: 21.9–23.5) in males and remained almost unchanged at 23.8% (95% CI: 22.9–24.6) in females (►Table 2, ►Fig. 2). In patients with LUAs, the mortality rates decreased form 30.1 (95% CI: 25.7–34.5) to 24.3% (95% CI: 22.1–26.5) in males and from 28.4 (95% CI: 24.7–32.1) to 24.2% (95% CI: 21.6–26.9) in females in the same period.

Discussion

Our analysis shows that the rates of cases hospitalized for ICB having LUAs do not follow the dramatic increase in LUA prescriptions and were much lower than the rates in all hospitalized cases, generally. The age-standardized mortality decreased continuously in those with LUAs but not in those without LUAs. This finding is all the more interesting as

Table 1 Gender-specific age-standardized proportions of patients with anticoagulation among hospitalized patients with and without I60/I61, Germany, 2006–2020

	All hospitalized cases without I60/I61			All hospitalized cases with I60/I61		
Year	Cases with anticoagulation[a]	All cases	Age-standardized proportions of cases with anticoagulation[b] (95% CI)	Cases with anticoagulation[a]	All cases	Age-standardized proportions of cases with anticoagulation[b] (95% CI)
Males						
2006	266,061	3,696,195	7.3 (7.3–7.3)	1,041	14,524	7.0 (6.5–7.4)
2007	307,783	3,829,611	8.2 (8.1–8.2)	1,255	14,767	8.2 (7.8–8.7)
2008	348,199	3,948,099	9.0 (8.9–9.0)	1,571	14,944	10.2 (9.7–10.7)
2009	395,130	4,069,876	9.9 (9.9–9.9)	1,693	14,721	11.1 (10.6–11.6)
2010	429,206	4,172,491	10.5 (10.4–10.5)	1,583	15,512	10.9 (10.4–11.4)
2011	468,658	4,285,188	11.1 (11.1–11.2)	1,790	15,071	11.4 (10.9–12.0)
2012	518,113	4,405,730	12.0 (11.9–12.0)	1,932	15,341	12.2 (11.6–12.7)
2013	574,544	4,485,581	13.0 (13.0–13.1)	2,124	15,430	13.2 (12.7–13.8)
2014	653,868	4,598,306	14.5 (14.5–14.5)	2,417	16,246	14.5 (13.9–15.1)
2015	717,707	4,702,323	15.6 (15.6–15.6)	2,172	16,582	12.6 (12.1–13.2)
2016	790,771	4,777,214	17.0 (16.9–17.0)	2,079	16,391	12.1 (11.5–12.6)
2017	854,078	4,858,479	18.1 (18.0–18.1)	2,113	16,517	12.1 (11.6–12.6)
2018	924,302	4,887,536	19.5 (19.5–19.5)	2,067	15,918	12.3 (11.8–12.9)
2019	1,007,251	4,995,100	20.8 (20.7–20.8)	2,266	16,231	13.4 (12.8–13.9)
2020	941,602	4,433,437	22.0 (21.9–22.0)	2,198	15,362	13.7 (13.1–14.3)
Females						
2006	242,058	4,330,273	5.6 (5.6–5.6)	942	16,268	5.6 (5.3–6.0)
2007	279,453	4,458,099	6.2 (6.2–6.2)	1,088	16,689	6.3 (5.9–6.7)
2008	317,518	4,579,632	6.8 (6.8–6.8)	1,354	16,696	7.5 (7.1–7.9)
2009	357,424	4,668,066	7.5 (7.4–7.5)	1,406	16,531	8.0 (7.5–8.4)
2010	387,510	4,736,357	7.9 (7.9–8.0)	1,465	16,816	7.9 (7.5–8.4)
2011	429,878	4,822,912	8.6 (8.6–8.6)	1,660	16,559	9.1 (8.7–9.6)
2012	474,608	4,907,488	9.3 (9.3–9.3)	1,692	16,743	9.2 (8.7–9.7)
2013	526,353	4,954,533	10.1 (10.1–10.1)	1,843	16,704	9.9 (9.4–10.4)
2014	602,340	5,048,069	11.3 (11.3–11.3)	2,049	17,114	10.8 (10.2–11.3)
2015	658,984	5,085,417	12.2 (12.2–12.3)	1,950	17,952	9.4 (9.0–9.9)
2016	728,668	5,126,454	13.4 (13.4–13.5)	1,939	17,466	9.6 (9.1–10.1)
2017	788,314	5,161,908	14.4 (14.3–14.4)	1,883	17,259	9.4 (8.9–9.8)
2018	849,844	5,129,426	15.6 (15.5–15.6)	1,995	16,794	10.1 (9.6–10.6)
2019	917,773	5,186,912	16.6 (16.5–16.6)	1,999	16,941	10.1 (9.6–10.5)
2020	846,482	4,488,541	17.7 (17.6–17.7)	2,055	16,288	10.8 (10.3–11.3)

Abbreviation: CI, confidence interval.
[a]Anticoagulation = ICD-10 code Z92.1 (long-term (current) use of anticoagulation).
[b]Reference population: hospitalized patients without I60/I61 in 2006.

in the ICB cases without LUAs such a significant decrease is not present. Age-standardized mortality remains unchanged in females and decreases only slightly in males in this group.

A Global Burden of Disease Study reported the incidence of stroke in 204 countries and territories from 1990 to 2019.[9] Ischemic stroke constituted 62.4% of all incidents of stroke in 2019, while ICB constituted 27.9% and subarachnoid hemorrhage (SAH) constituted 9.7%. In France, data from the National Stroke Action Plan reported a decrease in age-standardized rates of patients hospitalized for ischemic stroke by 1.5% in those aged ≥65 years from 2008 to 2014. The rate of patients hospitalized for ICB was stable (+2.0%).[10]

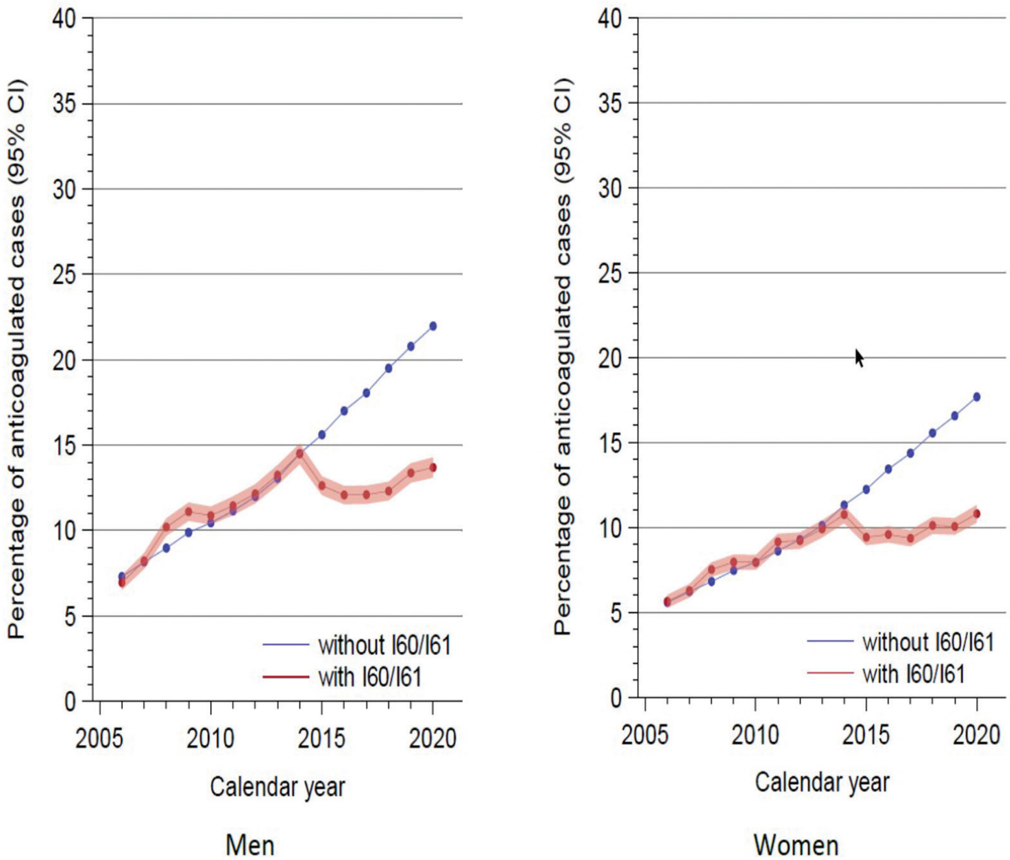

Fig. 1 Visualization of gender-specific age-standardized proportions of patients with anticoagulation among hospitalized patients with and without I60/I61, Germany, 2006–2020 I60: subarachnoid bleeding; I61: intracerebral bleeding; ICD-10 Z92.1 (long-term, current, use of anticoagulation); CI: confidence interval; weights for age-standardization from hospitalized patients without I60/I61 in 2006.

Table 2 Gender-specific age-standardized case fatality (%) in persons with I60/I61 stratified by long-term use of anticoagulation, Germany, 2006–2020

	Without long-term (current) use of anticoagulation[a]			With long-term (current) use of anticoagulation[a]		
Year	No. of dead persons with I60/I61	No. of persons with I60/I61	Age-standardized case fatality (%) in persons with I60/I61 (95% CI)[b]	No. of dead persons with I60/I61	No. of persons with I60/I61	Age-standardized case fatality (%) in persons with I60/I61 (95% CI)[b]
Males						
2006	3,088	13,483	24.1 (23.2–25.0)	301	1,041	30.1 (25.7–34.5)
2007	2,979	13,512	23.1 (22.2–23.9)	358	1,255	29.5 (25.5–33.6)
2008	2,927	13,373	22.6 (21.7–23.4)	395	1,571	23.2 (20.8–25.6)
2009	2,669	13,028	21.3 (20.5–22.1)	453	1,693	24.8 (22.4–27.2)
2010	2,849	13,776	21.2 (20.4–22.0)	467	1,736	25.2 (22.7–27.7)
2011	2,778	13,291	21.2 (20.4–22.0)	506	1,790	28.1 (25.3–30.8)
2012	2,792	13,409	21.0 (20.2–21.8)	520	1,932	26.0 (23.5–28.5)
2013	2,758	13,306	20.7 (19.9–21.5)	549	2,124	23.9 (21.7–26.1)
2014	2,843	13,829	20.5 (19.7–21.2)	643	2,417	24.5 (22.4–26.5)
2015	3,169	14,410	21.6 (20.8–22.4)	550	2,172	23.8 (21.6–26.0)
2016	3,073	14,312	21.0 (20.2–21.8)	504	2,079	21.5 (19.4–23.7)
2017	3,235	14,404	21.6 (20.9–22.4)	569	2,113	23.9 (21.6–26.2)
2018	3,047	13,851	21.2 (20.4–22.0)	534	2,067	23.0 (20.8–25.2)

Table 2 (*Continued*)

	Without long-term (current) use of anticoagulation[a]			With long-term (current) use of anticoagulation[a]		
Year	No. of dead persons with I60/I61	No. of persons with I60/I61	Age-standardized case fatality (%) in persons with I60/I61 (95% CI)[b]	No. of dead persons with I60/I61	No. of persons with I60/I61	Age-standardized case fatality (%) in persons with I60/I61 (95% CI)[b]
2019	3,201	13,965	21.9 (21.1–22.7)	548	2,266	20.4 (18.5–22.3)
2020	3,111	13,164	22.7 (21.9–23.5)	610	2,198	24.3 (22.1–26.5)
Females						
2006	4,009	15,326	23.9 (23.1–24.6)	306	942	28.4 (24.7–32.1)
2007	3,994	15,601	23.1 (22.4–23.9)	324	1,088	25.3 (22.2–28.5)
2008	3,816	15,342	22.3 (21.6–23.1)	424	1,354	27.0 (23.7–30.3)
2009	3,669	15,125	21.5 (20.8–22.3)	440	1,406	28.1 (24.9–31.2)
2010	3,718	15,351	21.4 (20.6–22.1)	430	1,465	24.6 (21.6–27.5)
2011	3,609	14,899	21.4 (20.7–22.2)	492	1,660	25.5 (22.6–28.4)
2012	3,684	15,051	21.3 (20.6–22.2)	492	1,692	24.3 (21.6–27.1)
2013	3,577	14,861	21.1 (20.3–21.8)	552	1,843	24.2 (21.6–26.8)
2014	3,643	15,065	21.2 (20.5–22.0)	598	2,049	25.0 (22.3–27.8)
2015	3,997	16,002	21.8 (21.1–22.5)	553	1,950	24.7 (21.8–27.7)
2016	3,827	15,527	21.2 (20.5–22.0)	566	1,939	22.9 (20.3–25.4)
2017	3,939	15,376	22.2 (21.4–22.9)	515	1,883	21.0 (18.5–23.5)
2018	3,895	14,799	22.8 (22.0–23.6)	566	1,995	22.7 (20.0–25.4)
2019	3,914	14,942	22.3 (21.5–23.1)	568	1,999	21.5 (19.1–24.0)
2020	3,844	14,233	23.8 (22.9–24.6)	645	2,055	24.2 (21.6–26.9)

Abbreviation: CI, confidence interval.
[a]Anticoagulation = ICD-10 code Z92.1 (long-term [current] use of anticoagulation).
[b]Reference population: hospitalized patients without I60/I61 in 2006.

According to the Danish Stroke Registry, the rates of ischemic stroke and ICB declined in people aged ≥50 years, but the rate of ICB remained constant at 11.2 to 11.4% in the period from 2005 to 2018.[11] The rate of anticoagulants in the ICB cases increased from 5.9 to 10.4%. Another report from Denmark reported that from 2005 to 2018, use of antithrombotic drugs, especially VKAs, was associated with ICB. Although use of oral anticoagulants (OACs) in the general population increased substantially during the study period from 3.8 to 11.1%, the incidence rate of ICB decreased.[12] An increase in the prescription rate of DOACs is reported worldwide.[13] Sheth et al analyzed British multisource health and prescription records data to investigate the association between prescription rate of DOACs and stroke/bleed events during the period from 2013 to 2016.[14] During the study period, the proportion of DOAC prescriptions increased at an average rate of 122% per annum. DOAC prescription **was associated** with 50% reduction in ischemic and hemorrhagic strokes. Among patients with atrial fibrillation (AF) with prior ICB, DOAC use was associated with lower rates of ICB and major bleeding compared with warfarin use, whereas the rate of ischemic stroke was similar in the two groups. A nationwide cohort study from Taiwan showed that compared with warfarin use, DOAC use was associated with a statistically significant lower risk of all-cause mortality and ICB.[15]

Our results show two different associations of ICBs and LUAs. First, the increase in LUAs is much lower in hospitalized ICB cases than in all the other cases. Second, mortality of ICB cases with LUAs decreases, whereas mortality in ICB cases without LUA does not.

We cannot really explain the first effect. As ICBs are triggered by LUAs, the rate of ICB in patients with LUAs should be higher than that in the general population. One possible explanation might be that the causes of LUA-associated ICBs and non-LUA-associated ICBs are different. The Oxford Community Stroke Project (OCSP; 1981–1986) and the Oxford Vascular Study (OXVASC; 2002–2006) reported exactly the opposite.[16] They reported that the incidence of ICB associated with premorbid hypertension dropped (0.37%; 95% CI: 0.20–0.69; $p = 0.002$), but the incidence of ICB associated with antithrombotic use increased (7.4%; 95% CI: 1.7–32; $p = 0.007$) resulting in substantially decreasing overall incidence of ICB (rate ratio: 0.53; 95% CI: 0.29–0.95; $p = 0.03$). Another explanation could be that preventive treatment of unruptured intracerebral aneurysm has increased.[17] Data from the National Inpatient Sample (2004–2014) were extracted, including patients with a primary

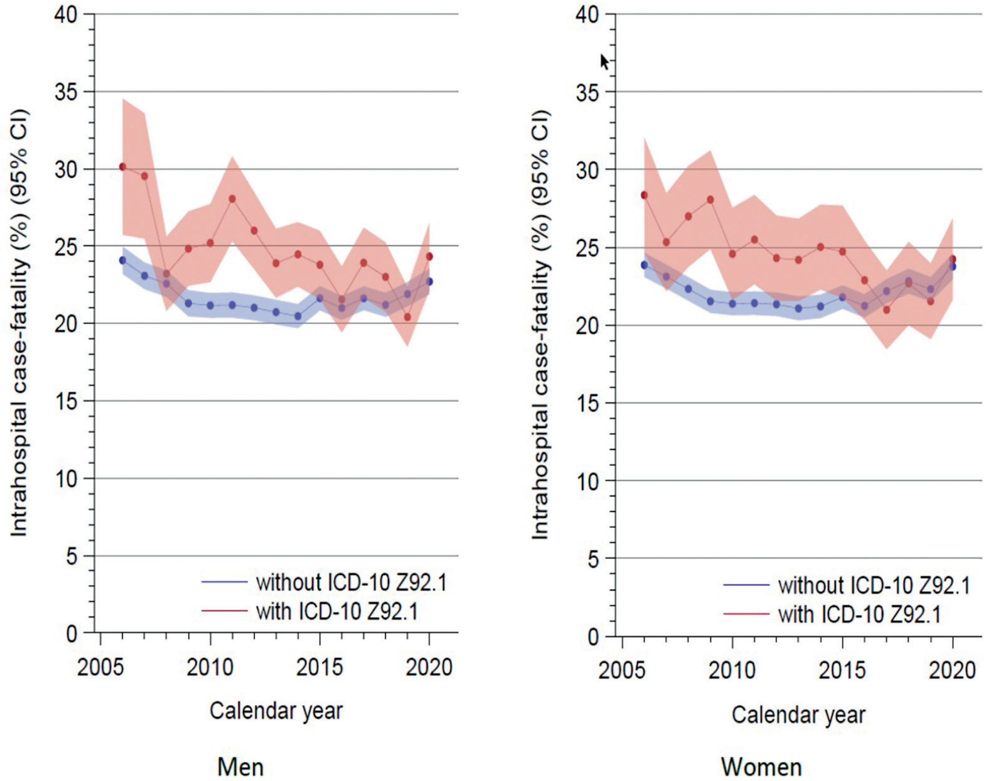

Fig. 2 Gender-specific age-standardized case fatality (%) in persons with I60/I61 stratified by long-term use of anticoagulation, Germany, 2006–2020. I60: subarachnoid bleeding; I61: intracerebral bleeding; ICD-10 Z92.1 (long-term, current, use of anticoagulation); CI: confidence interval; weights for age standardization from hospitalized patients without I60/I61 in 2006.

diagnosis of a subarachnoid bleeding (SAB) or unruptured intracranial aneurysms treated by clipping or coiling. With each passing year, there is a significant decrease in relative risk ratio of undergoing treatment for an SAB, concomitant with a stable annual risk of undergoing treatment for unruptured intracranial aneurysms. This trend is supported by a study from Korea carried out in the period from 2005 to 2015 using the nationwide database of the Korean National Health Insurance Service in South Korea. The marked increase in the detection and treatment of unruptured aneurysm (UA) might have contributed to the decreasing incidence of SAH.[18] Such an increase in preventive UA treatment should affect both groups of ICB cases, those with and those without LUAs. A third reason could be that the population treated with LUAs has changed to a healthier population. The change from C, Herzinsuffizienz" Herzinsuffizienz ("Congestive heart failure") 1; H, Hypertonie, auch behandelt ("Hypertension") 1; A, Alter >75 Jahre ("Age") 1; D, Diabetes mellitus ("Diabetes") 1; S2, Vorangegangener Schlaganfall oder transitorische ischämische Attacke" TIA ("Stroke") 2 (CHADS2 score) to Congestive heart failure (Herzinsuffizienz) 1 ; Hypertension 1; Age (>75 Jahre) 2; Diabetes mellitus 1; Stroke / TIA 2; Vascular disease (z.B. pAVK, vorangegangener Herzinfarkt, schwere Verkalkung der Aorta) 1; Age (65–74 Jahre) 1; Sex category (weibliches Geschlecht) 1 (CHA2DS2-VASc score) increases the rate of patients with AF who should have OACs from 66 to 94%.[19,20] AF patients were treated with LUAs because of minor criteria such as a female with other vascular diseases. It is unclear which of these three aspects have the largest impact on our findings. **Given the differences between our data and data from other countries, more information on the type of anticoagulation and primary diagnosis as well as cause of bleeding in patients without anticoagulation would be necessary.**

The second finding might be explained by the differences in stroke volume associated with DOACs. Patients with DOAC ICB showed lower ICB volume and better clinical outcomes than patients with warfarin ICB.[21] The onset of warfarin ICB was frequently observed in the morning and evening delaying diagnosis and treatment, whereas DOAC ICB did not show any specific onset time. In contrast, there is lack of a decrease in age-standardized mortality in female ICB cases without LUAs and only a slight decrease in males in the observation period of 15 years, which is more difficult to explain. A population-based study from South Texas reported a decrease in ICB incidence, but an unchanged case fatality and long-term mortality in the period from 2000 to 2010.[22] A systematic review from 2019 reported no significant reduction of mortality at 1 month (–0.4% per year; 95% CI: –1.0 to 0.2; $p = 0.155$) in the last three decades.[23] A population-based cohort study from Denmark analyzed the mortality in ICB patients from 2004 to 2017 and found an improvement over time in the unadjusted mortality rate after 30 days.[24] They discussed the changes in the risk profile, the increasing proportion of less severe strokes, and improvements by early admission of ICB patients to specialized stroke care units as possible explanations. Such effects should have influenced the ICB mortality in patients without LUAs in Germany as well.

Strength and Limitation

A major strength of this study is the large data set, which includes virtually all German hospitals. 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.

However, there are factors that limit our results. First, our study design did not allow control for confounding including indications for treatment, quality of treatment, polypharmacy, and relevant comorbidities. Second, the analyses are not on a per-patient basis, and patients may be included multiple times. Moreover, the DRG data do not allow for the differentiation between first-line treatments and revision procedures. Third, we cannot assess if and how coding errors may have impacted our analysis. Thus, undercoding can be assumed, especially for the use of anticoagulants (ICD code Z92.1)

Conclusion

Our results show that the increase in LUAs in ICB cases is much lower than that in the general hospitalized population. We also found a decrease in intrahospital mortality rates in ICB cases with LUAs from 2006 to 2020, but not in ICB cases without LUAs. We cannot explain the specific reasons for these differences, and further research is needed with better knowledge of the cases.

Author Contributions

K.K. contributed to the conception and design of the study, acquisition of data (laboratory or clinical), drafting of the article and/or critical revision, and final approval of the manuscript.

F.H. and K.F. contributed to the conception and design of the study, acquisition of data (laboratory or clinical), analysis of data, drafting of the article and/or critical revision, and final approval of the manuscript. L.F. contributed to the conception and design of study, drafting of the article and/or critical revision, and final approval of the manuscript. B.K. contributed to the conception and design of the study, analysis of data, drafting of the article and/or critical revision, and final approval of the manuscript. A.S. contributed to the conception and design of the study, drafting of the article and/or critical revision, and final approval of the manuscript.

Compliance with Ethical Standards

The authors declare that they have no potential conflicts of interest and include no research involving human participants and/or animals.

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None.

Conflict of Interest

The authors declare that they have no conflict of interest.

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