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ANTICOAGULANT-RELATED GASTROINTESTINAL BLEEDING: A REAL-LIFE DATA ANALYSIS ON BLEEDING PROFILES, FREQUENCY AND ETIOLOGY OF PATIENTS RECEIVING DIRECT ORAL ANTICOAGULANTS VERSUS VITAMIN K ANTAGONISTS

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Vitamin K antagonists (VKA) continue to be the standard of long-term anticoagulation. Direct oral anticoagulants (DOAC) are increasingly used. In many trials DOAC were at least as effective as VKA. In this study we evaluate the bleeding profiles, frequencies and etiologies of patients receiving DOAC versus VKA in a real-life setting. All patients presenting with suspected gastrointestinal bleeding (GIB) in the emergency department of the University Hospital Erlangen in one year were enrolled in this study. They were looked up for the intake of either DOAC (dabigatran, rivaroxaban and apixaban) or VKA. The results showed that 406 patients with suspected GIB were admitted to the emergency unit of the University Hospital Erlangen. In 228 of those patients GIB could be verified (56.2%). Fifty four of those patients (23.7%) were administered either VKA or DOAC. In 35 of those 54 patients (64.8%) GIB was classified as 'major bleeding'. In 27 patients with administration of VKA upper GIB was recorded and lower GIB was detected four times. In 16 patients with administration of DOAC upper GIB was found and lower GIB was found in 7 patients. The presented data do not show higher GIB rates for DOAC (mainly dabigatran and rivaroxaban), but do also not indicate a significantly higher safety of DOAC concerning GIB than VKA. This finding represents a clear contrast to the reduced bleeding rates of DOAC for intracerebral bleeding and other non-GIB events. According to our study, the absolute number of DOAC-associated GIB events is lower than in the VKA group.

Key words: *gastrointestinal bleeding, bleeding profiles, bleeding management, vitamin K antagonists, direct oral anticoagulants, real-life data*

INTRODUCTION

For many decades, vitamin K antagonists (VKA) have been the standard of long-term anticoagulation in indications such as stroke prevention in atrial fibrillation and treatment of venous thromboembolism (VTE). The significant inter-individual variations in metabolism, numerous drug-drug interactions and the interaction with dietary intake of vitamin K can cause problems in VKA therapy (1). In addition, routine monitoring of the anticoagulation intensity is necessary. Thromboembolic as well as bleeding complications associated with VKA are common. Annual rates of major bleeding in VKA patients in daily care are estimated to be up to 8% (2-4). Direct oral anticoagulants (DOAC) include the direct thrombin inhibitor dabigatran and the anti-Xa agents rivaroxaban, apixaban and edoxaban. They are increasingly used in the prevention of stroke in patients with non-valvular atrial fibrillation and in the prevention and treatment of venous thromboembolism in many countries. In numerous phase III clinical trials DOAC were at least as effective as VKA (5-9). They were associated with a similar or lower incidence of major bleeding events, including consistent and significant decreases in intracranial bleeding, although with an increase in gastrointestinal bleeding (GIB) for some agents like rivaroxaban or dabigatran compared with VKA in certain studies (10). Also metaanalyses from studies have shown a slightly increase in GIB events in patients receiving DOAC (11, 12). In contrast, in meta-analyses DOAC used in the treatment of VTE was associated with a significantly lower risk of bleeding complications (13, 14).

However, the occurrence rate of GIB events in real-life conditions with several intervening variables like age, use of non-steroidal anti-inflammatory drugs (NSAID) and other co-medications, presence of ulcer disease, renal insufficiency, unapparent hematological or other neoplastic diseases *etc.* has not yet been extensively analyzed. First real-life studies have supported the efficacy and safety of DOAC also in routine clinical practice (11, 12, 15), but data on GIB events are scarce. Nevertheless, because of the published data physicians may still have concerns about GIB or emergencies. However, in daily clinical practice the exact risk of these events is not clearly known because randomized clinical trials often have stringent inclusion and exclusion criteria, thus excluding certain groups of patients according to their age or pre-existing disease or malignancies, respectively. Hence, results of those trials may not be fully

reflective of, or universally applicable to, the real-life patient population. In addition, routine follow-up evaluations of the indication for the use of DOAC or VKA are often missed. It is the aim of this work to evaluate the exact bleeding profiles, frequencies and etiologies of patients receiving DOAC versus VKA in a real-life setting. Therefore, all patients with suspected GIB referred to the emergency department of the University Hospital Erlangen in the year 2014 were retrospectively analyzed.

MATERIAL AND METHODS

All patients presenting with suspected GIB in the emergency department of the University Hospital Erlangen in the year 2014 were enrolled in the study. They were looked up for the intake of either DOAC (dabigatran, rivaroxaban and apixaban) or VKA. Data acquisition was performed by searching for the following ICD-codes: K92.0/K92.1/K92.2 and Z92.1 given as GIB, melena, hematemesis and anticoagulation therapy. The obtained data were entered into a registry and for further analysis retrospectively evaluated using IBM SPSS Version 21.0 (IBM Corporation, Armonk, NY, USA).

The study was conducted according to the declaration of Helsinki and approved by the institutional review board (Clinical Ethics Committee at the University Hospital Erlangen, 22.10.2013) and written, informed consent was obtained from each patient included in the study.

The following details were evaluated: age, gender, anticoagulants (none, VKA, DOAC), endoscopic intervention, causes of GIB, transfusion of blood and blood products, CHA2DS2-VASc and HAS-BLED score. GIB was classified according to the American Gastroenterological Association (AGA) (16). Upper GIB (UGIB) includes hemorrhage originating from the esophagus to the ligament of Treitz (17), mid GIB (MGIB) was defined as bleeding coming from the small bowel between the ligament of Treitz to the terminal ileum and lower GIB coming from the colon (16). Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria as clinically overt bleeding accompanied by a decrease in hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intraarticular, intramuscular with compartment syndrome, pericardial, retroperitoneal), or resulting in death (18). From all patients with

Table 1. Patients' characteristics.

	Overall (n = 406)	**confirmed GIB** (n = 228)	**confirmed GIB and VKA** (n = 31)	**confirmed GIB and DOAC** (n = 23)
median age, years (Range)	71 (18 – 94)	68 (18 – 92)	73 (60 – 87)	77 (56 – 92)
male	n = 210 (51.7%)	n = 119 (52.2%)	n = 17 (54.8%)	n = 10 (43.5%)
female	n = 196 (48.3%)	n = 109 (47.8%)	n = 14 (45.2%)	n = 13 (56.5%)
Hb (mg/dl)	9.6 (± 3.5)	9.5 (± 3.3)	8.4 (± 2.9)	8.9 (± 2.6)
PPI	n = 134 (33.0%)	n = 84 (36.8%)	n = 12 (38.7%)	n = 11 (47.8%)
NSAID	n = 30 (7.4%)	n = 25 (11.0%)	n = 1 (3.2%)	n = 2 (8.7%)
corticosteroids	n = 21 (5.2%)	n = 15 (6.6%)	–	–
ASA	n = 103 (25.4%)	n = 66 (28.9%)	n = 7 (22.6%)	n = 9 (39.1%)
Clopidogrel	n = 32 (7.9%)	n = 17 (7.5%)	n = 3 (9.7%)	n = 1 (4.3%)
Prasugrel	n = 2 (0.5%)	n = 2 (0.9%)	–	–
Ticagrelor	n = 3 (0.7%)	n = 2 (0.9%)	–	–
LMWH	n = 8 (2.0%)	n = 7 (3.1%)	–	–
VKA	n = 48 (11.8%)	n = 31 (13.6%)	n = 31 (100%)	–
dabigatran	n = 4 (1.0%)	n = 2 (0.9%)	–	n = 2 (8.7%)
rivaroxaban	n = 26 (6.4%)	n = 20 (8.8%)	–	n = 20 (87.0%)
apixaban	n = 2 (0.5%)	n = 1 (0.4%)	–	n = 1 (4.3%)
atrial fibrillation	n = 88 (21.7%)	n = 53 (23.2%)	n = 23 (74.2%)	n = 18 (78.3%)

Abbreviations: Hb, hemoglobin; UGIB, upper gastrointestinal bleeding; LGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants; PPI, proton pump inhibitors; NSAID, nonsteroidal anti-inflammatory drugs; LMWH, low-molecular-weight heparin; ASA, acetylsalicylic acid.

suspected GIB actual complete diagnostics with medical history, physical examination, blood count, ultrasonography, endoscopy of the upper and lower GI-tract and other diagnostic modalities was performed. If GIB could not be verified, those patients were excluded from further statistical analysis as they did not meet the inclusion criteria of confirmed GIB.

RESULTS

Demographic results, confirmation of bleeding rate and anticoagulation groups 406 patients with suspected GIB were admitted to the emergency unit of the University Hospital Erlangen in the year 2014. *Table 1* summarizes the patients' characteristics. In 228 of those patients a GIB according to the AGA criteria could be verified (228 patients of 406; 56.2%). Fourty eight of all admitted patients with suspected GIB were administered VKA (48 patients of 406, 11.8% of the whole population) and 32 of all admitted patients were administered DOAC (32 patients of 406; 7.9% of the whole population). However, among this whole population admitted to the emergency department in 2014 (n = 406) GIB was confirmed among all VKA patients in only 31 of 48 cases (64.6%), while GIB manifested among all DOAC patients in a comparable rate with 23 of 32 cases (71.9%).

Analyses of bleeding patients

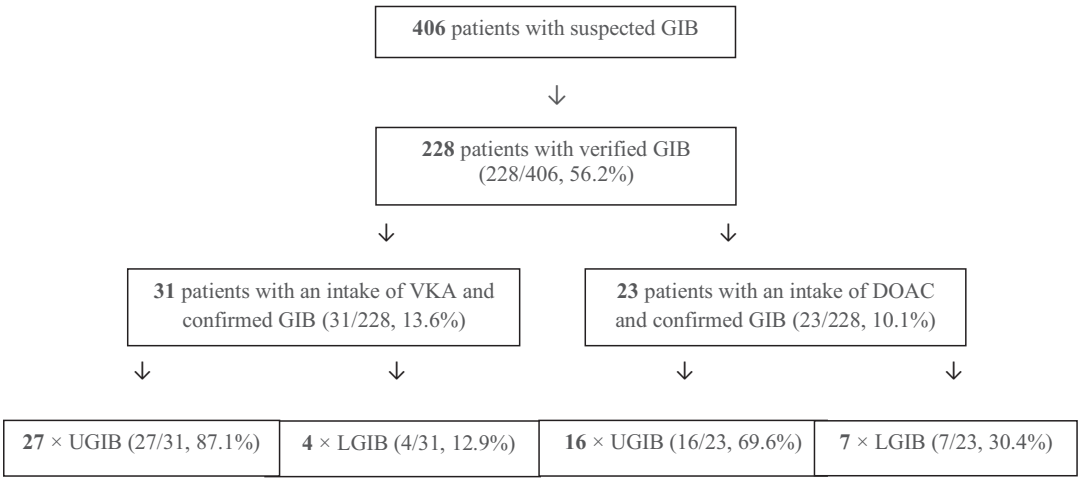
After completion of diagnostics GIB could be verified in total in 54 of 228 GIB patients (23.7%), taking either VKA in 31 of 228 patients (13.6%) or DOAC in 23 of 228 patients (10.1%), respectively. *Table 2* (flowchart) shows the distribution of bleeding patients in each group with a detailed analysis of patients who presented with upper or lower GIB.

Table 3 summarizes the exact pathological findings for each anticoagulant group (multiple mentions possible). Most of the other patients presenting with confirmed GIB (n = 159; 69.7%) were found to have medication intake of either acetylsalicylic acid (ASA), P2Y12 inhibitors (*e.g.* clopidogrel, prasugrel or ticagrelor), low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), or combinations thereof, respectively. Only a small proportion of patients (n = 15; 6.6%) presented with confirmed GIB without any coagulation intervening agents.

Comparison of gastrointestinal bleeding events in vitamin K antagonists and direct oral anticoagulants groups

From all bleeding events in 54 patients, 35 of 54 patients (64.8%) had GI-bleedings classified as 'major bleeding' according to ISTH (3). These 35 events of 'major bleeding' in

Table 2. Flowchart.



GIB, gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding; LGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants.

Table 3. Different bleeding lesions in VKA and DOAC patients.

	UGIB and LGIB			
anticoagulant	**VKA**	**dabigatran**	**apixaban**	**rivaroxaban**
erosion	n = 15	–	–	n = 10
ulcer	n = 9	n = 2	n = 1	n = 5
angiodysplasia	n = 11	–	–	n = 7
carcinoma	n = 5	–	–	n = 1
varices	n = 1	–	–	–
anal fissure	–	–	–	n = 1
hemorrhoids	–	–	–	n = 1
Total number	**n = 41**	**n = 2**	**n = 1**	**n = 25**

UGIB, upper gastrointestinal bleeding; LGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants.

Table 4. Pathological lesions in patients with VKA and DOAC intake (multiple mentions possible) classified for the upper and lower gastrointestinal tract.

location	**UGIB**		**LGIB**	
anticoagulant	**VKA**	**DOAC**	**VKA**	**DOAC**
erosion	n = 15	n = 7	-	n = 3
ulcer	n = 8	n = 7	n = 1	n = 1
angiodysplasia	n = 10	n = 6	n = 1	n = 1
carcinoma	n = 2	–	n = 3	n = 1
varices	n = 1	–	–	–
anal fissure	–	–	–	n = 1
hemorrhoids	–	–	–	n = 1
Total number	**n = 36**	**n = 20**	**n = 5**	**n = 8**

UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants

Table 5. Topographical bleeding locations in patients with VKA and DOAC intake (multiple mentions possible).

location	esophagus		stomach		duodenum		jejunum/ileum		colon		rectum	
anticoagulant	**VKA**	**DOAC**	**VKA**	**DOAC**	**VKA**	**DOAC**	**VKA**	**DOAC**	**VKA**	**DOAC**	**VKA**	**DOAC**
erosion	n = 2	n = 2	n = 10	n = 3	n = 3	n = 2	–	n = 1	–	n = 2	–	–
ulcer	n = 1	–	n = 6	n = 7	n = 1	–	n = 1	–	–	n = 1	–	–
angiodysplasia	–	–	n = 8	n = 4	n = 2	n = 2	–	–	n = 1	n = 1	–	–
carcinoma	–	–	n = 2	–	–	–	–	–	n = 3	–	–	n = 1
varices	n = 1	–	–	–	–	–	–	–	–	–	–	–
anal fissure	–	–	–	–	–	–	–	–	–	–	–	n = 1
hemorrhoids	–	–	–	–	–	–	–	–	–	–	–	n = 1
Total number	n = 4	n = 2	n = 26	n = 14	n = 6	n = 4	n = 1	n = 1	n = 4	n = 4	n = 0	n = 3

VKA, vitamin K antagonists; DOAC, direct oral anticoagulants

228 patients (15.4%) resulted from major bleeding in 21 of 228 patients with an intake of VKA (9.2%) and 14 of 228 patients with an intake of DOAC (6.1%), respectively. Interestingly, among all confirmed bleeding episodes in the DOAC group, 20 of 228 patients (8.8%) were found on rivaroxaban medication, while 2 of 228 patients (0.9%) had dabigatran and only 1 patient of 228 (0.4%) was on apixaban treatment (*Table 2*). Although DOAC showed a tendentially lower overall bleeding rate (10.1% versus 13.6%) and lesser events of 'major bleeding' (6.1% versus 9.2%), the difference was not statistically significant. This was also the case in thromboembolic and bleeding risk scores between both groups. The median CHA2DS2-VASc-Score (calculating the stroke risk factors in patients with atrial fibrillation) was 4 points in the VKA group versus 5 points in the DOAC group. Similarly, there was also no significant difference in the HAS-BLED Score (estimating the risk of major bleeding for patients on anticoagulation for atrial fibrillation) for VKA and DOAC patients with 4 and 3 points, respectively.

Analysis of exact bleeding locations and pathological lesions in patients with vitamin K antagonists and direct oral anticoagulants throughout the gastrointestinal tract

Table 4 summarizes the different bleeding sources. Among the 31 patients with confirmed GIB and administration of VKA UGIB was recorded in 27 cases (27 of 31 patients, 87.1%, see *Table 2*). Lower GIB (LGIB) was detected four times in this group (4 of 31 patients, 12.9%, see *Table 2*). In total, 36 UGIB lesions were found in 27 patients (1.3 bleeding lesions per patient) arising from the esophagus, stomach, or duodenum (*Tables 4* and *5*, multiple mentions possible). LGIB lesions were documented five times in the 31 patients with administration of VKA (1.2 bleeding lesions per patient) (*Tables 4* and *5*, multiple mentions possible). Interestingly, among the 23 patients with confirmed GIB and administration of DOAC, the UGIB was found in 16 patients (69.6%, see *Table 2*) with a frequency of 20 lesions (1.3 bleeding lesions per patient, *Tables 4* and *5*, multiple mentions possible). LGIB was found in 7 patients (30.4%, see *Table 2*) respectively in this group with a total number of 8 bleeding lesions (1.1 bleeding lesions per patient, *Tables 4* and *5*, multiple mentions possible). This means that LGIB was seen in a somewhat higher frequency in the DOAC group with 7 of 23 patients (30.4%) with n = 8 lesions compared to 4 of 31 patients (12.9%) in the VKA group with n = 5 lesions (n.s.). Analysis and type of lesions in the groups with VKA, DOAC are shown in *Table 5*. Furthermore, six cases of undiagnosed carcinomas could be identified because of the GIB event (two gastric carcinomas and four colorectal carcinomas). Anticoagulation induced tumor bleeding was found in 5 patients with VKA (5/31 patients, 16.1%) and in 1 patient with DOAC (1/23 patients, 4.3%).

DISCUSSION

The use of anticoagulants (VKA and DOAC) in prevention of stroke in patients with nonvalvular atrial fibrillation and in the prevention and treatment of venous thromboembolism is becoming more frequent. Large randomized controlled trials now have shown that DOAC have favorable efficacy and safety characteristics compared with VKA whilst being at least as effective as the conventional VKA-treatment *inter alia* in preventing recurrent venous thromboembolism (19). However, beyond this there is also preclinical data demonstrating that DOAC alter fibrin clot properties and it remains unclear whether these drug-induced changes may contribute to bleeding risk in

patients taking anticoagulants such as DOAC (19). Especially because one of the main side effects of these drugs is the occurrence of GIB. And furthermore, although similar in many aspects, the essential DOAC trials differ in study design and study population, and their results are not directly comparable to real-life observations and between each other (6, 9, 20). In our study major GIB, one of the principal safety endpoints, was defined according to the ISTH criteria and we identified two patients with a major GIB in patients given dabigatran, one of them with an ulcer in the stomach and the other one with a rectal ulcer. Major GIB particularly occurred during the first few months of treatment. Dabigatran-related major GIB was higher with the concomitant administration of antiplatelet therapy such as ASA or P2Y12 inhibitors (*e.g.* clopidogrel, prasugrel or ticagrelor), and with decreasing creatinine clearance. In patients > 75 years, the risk of major GIB was higher with dabigatran than with warfarin, whereas in patients aged < 65 years, the risk of major GIB was higher with warfarin (21). The specific bleeding lesions were not reported. We identified 12 major GIB and 8 minor GIB in patients given rivaroxaban, mostly located in the stomach or the proximal duodenum. In the ROCKET-AF trial rivaroxaban was associated with a significantly increased rate of major GIB as compared with warfarin (3.2% versus 2.2% per year; $P < 0.001$) (9, 22). The anatomic locations of the GIB were not specified. An increased rate of GIB was noted *inter alia* in individuals receiving concurrent antiplatelet therapy, older individuals, individuals with lower creatinine clearance, those with anemia at baseline and those who had experienced a prior stroke. We identified one minor GIB in patients given apixaban, which was located in the in the stomach. In the ARISTOTLE trial the major GIB rates were numerically, but not statistically significantly lower in the apixaban group compared with the warfarin arm (n = 121 versus n = 133) (6). In the AVERROES trial of apixaban compared with low-dose ASA major GIB rates were comparable in the apixaban and ASA arms (7). Altogether in our real-life data from 2014 from a tertiary referral center at a University hospital 14.6% of patients suffering from confirmed GIB were on VKA compared with 10.8% in patients who were administered DOAC. This difference was not statistically significant. The observed elevated rate of GIB in patients receiving VKA could be influenced by the more frequent use of VKA in daily life, its known problems of adjusting the adequate dose and various intervening variables (23). Abraham *et al.* also reported in their study that the risk of GIB related to DOAC was similar to that for VKA (24). Although the occurrence of GIB compared with VKA was controversially reported for dabigatran and rivaroxaban in prospectively monitored studies, case reports or real-life registries, respectively, (25-27) our analysis has the advantage to focus on unselected consecutive patients from one year presenting real-life data without applying any special exclusion criteria. Thus, we are able to present important real-life data incorporating every day patients with their associated comorbidities and inherent risks. Our retrospective analysis shows that in this cohort with a total of 228 GIB-events, bleeding occurs in patients taking VKA in a frequency of 13.6%, while bleeding rate was not significantly lower in DOAC patients (10.1%). On the second view, the critical observation that from all GIB events in patients administered VKA 21 of 31 GIB events (67.7%) were major bleedings compared to 14 of 23 GIB events (60.9%) in patients receiving DOAC gives further hints for critical considerations. The relatively high incidence of rivaroxaban associated GIB in our study should be interpreted with caution as in 2014 rivaroxaban was clearly more frequently prescribed than the other two DOAC in Germany. Although quantitatively more lesions were found in the rivaroxaban treated patients similarly for the upper and lower GI tract, there was no qualitative difference to VKA patients or the other two DOAC. Compared with the above cited frequencies of GIB (3.2 – 1.5%) in the DOAC registration studies the events of major GIB was nearly 4-5-fold higher in our real-life analysis than suggested by these trials (6, 7, 9). Thus, albeit DOAC have a significant benefit for patients concerning their safety profile for all-cause mortality, intracerebral bleeding or all-cause major bleeding (6, 7, 9), GIB remains a further critical drawback, irrespective of whether type of anticoagulant is used. Thus, in an effort to improve future anticoagulation therapy in terms of safety, the evaluation of patients for DOAC, all measures to prevent GIB and awareness of potential bleeding lesions will become an essential task for cardiologists, neurologists to interact with gastroenterologists. Similarly as found in the registration trials, the rate of LGIB during DOAC treatment was numerically increased in our analysis. VKA was found to induce a rate of 12.9% of LGIB whilst DOAC had a bleeding rate of 30.4% in the lower GI-tract. In contrast to the increased LGIB rate induced by dabigatran - relative to warfarin - in the Re-LY study, which has been associated with higher intraluminal dabigatran concentrations in the GI-tract (2), we could not observe a difference between UGIB and LGIB in patients administered dabigatran. However, this may be related to the fact that meantime application, dosing, awareness of kidney function and interactions of dabigatran have been more precisely learnt than at the beginning of the dabigatran era where most reports on GIB came from this time involving often elderly patients (11, 28). For all DOAC the most common bleeding sources in upper GI-tract include erosions, peptic ulcers and angiodysplasia. Besides these above-mentioned bleeding sources, LGIB also involves anal fissures, hemorrhoidal bleeding and colorectal neoplasia. In our study except of erosions, the most frequent bleeding source were angiodysplasia that appeared in all parts of the GI-tract. Future trials should draw special attention to this finding because it has been shown that patients presenting with anemia or iron deficiency prior to anticoagulation have an augmented bleeding risk (6). In addition, a recent finding from double balloon endoscopy reported on the significantly increased rate of small bowel angiectasia bleeding in patients with cardiovascular disease and lipid islets (29), a patient population often subjected to anticoagulation medications. We could not observe a significant difference between upper and lower GIB for both groups (VKA vesus DOAC). Altogether, UGIB was a little more frequent in patients administered VKA (87.1/69.6%). In summary the administration of VKA and DOAC was found to enhance the incidence of GIB, which is in our real-life population clearly higher than in the registration trials (6, 7, 9). The presented real-life data of patients do not show higher GIB rates for DOAC (mainly dabigatran and rivaroxaban in our study), but presently the data do also not indicate a significantly higher safety of DOAC concerning GIB than VKA, which is a clear contrast to the reduced bleeding rates of DOAC for intracerebral bleeding and other non-GI major bleeding events. Even if the absolute number of all GIB events is lower in DOAC patients than in VKA treated patients, LGIB was confirmed to occur in an equal or higher frequency than in VKA patients in our survey. Thus, GIB remains a further worthwhile and important parameter to be judged in patients with the indication for anticoagulant therapy. As DOAC therapy has its clear and significant advantage to reduce intracranial bleeding and other types of major bleeding except GIB DOAC therapy is to be preferred and recommended in most patients receiving a new anticoagulant therapy (30). Still, choosing the right anticoagulant for the right patient is of outmost importance. In these efforts, one must also consider the fact that the bioavailability of DOACs is potentially susceptible to pharmacogenetics variation. Several gene polymorphism of proteins have the potential to affect their metabolism and thus their side effects such as bleeding events (31). Therefore, it must be stated that each physician has to evaluate each patient

carefully for the potential presence of GIB lesions, either before anticoagulant therapy or during such a therapy if any warning signs become evident, like positive fecal occult blood, iron deficiency, anemia, abdominal disturbances, dyspepsia or melena.

Study limitations

Limitations of this study are its rather small sample size, the retrospective nature of the study, the short period of follow up and the dependency of the DOAC use on the distribution of each DOAC on the German market. Furthermore we only show date from one tertiary referral center. Despite these limitations, our investigation also has much strength, including our inclusion of a diverse, real world population. Therefore these real-life data give a very good summary about realistic expectations in daily clinical routine and demonstrate the difference between GIB events in the controlled registration trials and real-life data.

Conflict of interests: None declared.

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