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DISSERTATION

Retrospective study of etiology and treatment outcomes of patients with gastrointestinal bleedings with focus on exposure to vitamin K antagonists and new oral anticoagulants in a community care hospital in Saxony

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1. Zusammenfassung

Die aktuelle retrospektive, monozentrische Studie stellt Ätiologie sowie Therapieergebnisse der gastrointestinalen Blutungen (GIB) dar und ist auf die Therapie mit oralen Antikoagulanzien fokussiert.

GIB sind mit einer hohen Morbidität und Mortalität assoziiert und stellen die Krankenkassen vor finanzielle Herausforderungen. Zudem sind sie mit einer hohen Letalität, insbesondere bei den älteren und multimorbiden Patienten vergesellschaftet. Bei diesen Patienten, die aufgrund einer anderen Erkrankung hospitalisiert sind, treten häufig Rezidivblutungen auf. Die flexible Endoskopie des Gastrointestinaltraktes spielt bei der Diagnostik und Behandlung einer GIB die Hauptrolle.

Eine Antikoagulationstherapie ist ebenfalls mit dem Risiko einer GIB assoziiert - unabhängig davon, ob Vitamin K Antagonisten (VKA) oder neue (direkte) orale Antikoagulanzien (NOAKs) verwendet werden. Die randomisierten kontrollierten Zulassungsstudien aller NOAKs ergaben vergleichbare oder höhere GIB Häufigkeit im Vergleich zu den VKA. Eine prospektive randomisierte Studie von verschiedenen NOAKs im Bezug auf GIB wurde bisher nicht durchgeführt.

Die aktuelle, retrospektive Beobachtungsstudie führte ich im Kreiskrankenhaus in Meißen (Sachsen) durch. Vom Januar 2012 bis Dezember 2014 wurden 830 Patienten eingeschlossen; 55.2% mit einer oberen, 42.5% mit einer unteren GIB aus dem Rektum und Kolon, 0.8% mit einer Dünndarmblutung und 1.5% zeigten eine GIB unklarer Herkunft. Die endoskopische Behandlung war in 21.8% Fällen indiziert; 2.6% Patienten wurden chirurgisch operiert. In 24.2% trat die GIB bei den Patienten auf, die mit oralen Antikoagulantien behandelt wurden. Darunter waren 13.9% VKA und 10.4% NOAKs. 35.2% Studienpatienten nahmen Thrombozytenaggregationshemmer ein, allerdings war die Kombinationstherapie bestehend aus einem VKA/NOAK und einem oder zwei Thrombozytenaggregationshemmer selten und betrug 1.9% und 0.8%.
Patienten in der Antikoagulationsgruppe waren mit 77.8±9.0 Jahren älter im Vergleich zur Kontrollgruppe (Durchnittsalter: 70.9±16.2 Jahre). Patienten der Antikoagulantien-Gruppe hatten häufiger die folgenden Komorbiditäten: koronare Herzerkrankung (29.9%), Diabetes mellitus (36%) oder ein Malignom (14.9%).

Peptischen Läsionen im oberen GI Trakt waren die häufigste Blutungsquelle in den beiden Studiengruppen. Eine aktive Blutung zum Zeitpunkt der Endoskopie war gleich häufig bei Patienten mit und ohne Antikoagulationstherapie (7.5% und 10.5%).

Eine Transfusion von Blutprodukten (inklusive Prothrombinkonzentraten) war in beiden Studiengruppen vergleichbar: 45.8% (Antikoagulation) und 42.8% (Kontrollen). Die Patienten erhielten durchschnittlich 1.8 und 1.6 Erythrozytenkonzentrate. Weder die Klinikaufenthaltsdauer (10.2 und 10.1 Tagen) noch die Aufenthaltsdauer auf Intensivstation (6.5 und 6.1 Tagen) unterschieden sich zwischen den beiden Studiengruppen.

Bei 6.6% der Fälle fand eine Rezidivblutung während desselben Klinikaufenthaltes statt. Bei weiteren 3.3% der Patienten trat eine Rezidivblutung innerhalb von 30 Tagen nach der Krankenhausentlassung auf; es war jedoch kein Unterschied zwischen der Antikoagulations- und Kontrollgruppe detektierbar. Die Rezidiv-GIB waren hierbei mit einer hohen Mortalität assoziiert: 34.5% Patienten mit Rezidivblutung verstarben, verglichen mit 4.4% ohne. Patienten, die aufgrund einer anderen Erkrankung stationär behandelt wurden und eine GIB hatten, hatten auch eine deutlich höhere Mortalität (21%).

Eine Niereninsuffizienz (GFR<30ml/h) bei Klinikaufnahme war mit einer hohen Mortalität von 16.7% assoziiert, verglichen mit 4.6% bei Patienten mit einer GFR>30ml/h. Patienten der NOAK-Gruppe und gleichzeitig einer GFR<30ml/h bei Klinikaufnahme zeigten vergleichbar häufig eine Rezidivblutung, aktive GIB während Endoskopie, Transfusionsbedarf und Mortalität, wie solche mit GFR>30ml/h, VKA oder Antikoagulations-naiven Patienten.

Überraschenderweise war die Mortalität signifikant niedriger bei den Patienten der Antikoagulationsgruppe (3.5%) im Vergleich zu Patienten ohne Antikoagulantien (7.3%). Die GIB war die Todesursache in 24.6% der Fälle, die weiteren häufigsten Todesursachen waren Infektionen (20%) und bösartige Tumore (15.4%).

Die Therapieergebnisse der gastrointestinalen Blutungen bei den Patienten mit und ohne orale Antikoagulanzien waren vergleichbar mit den bereits veröffentlichten Studien. Die Daten aus der aktuellen retrospektiven Observationsstudie sprechen dafür, dass die VKA und NOAKs auch bei älteren und multimorbiden Patienten mit einem vergleichbar hohen GIB Risiko assoziiert sind.

Die beobachtete, niedrigere Mortalität in der Antikoagulationsgruppe der aktuellen Studie ist möglicherweise durch die Verordnung der Therapie an initial gesündere Patienten bzw. jene, mit

niedrigerem GIB-Risiko zu erklären. Dieses Bias sollte in den Beobachtungsstudien berücksichtigt werden.

2. Conclusion

This retrospective single-center study presents gastrointestinal bleeding (GIB) etiology and treatment outcomes with special focus on oral anticoagulation.

GIB is a major source of morbidity, mortality and has a high economic burden. Fatal outcomes of GIB are highest in elderly, multimorbid patients as well as those with recurrent GIB. Inpatients who developed GIB while being hospitalized for another health problem have a high mortality, as well. The mainstay of GIB diagnosis and treatment is flexible endoscopy.

Anticoagulation is associated with GIB regardless of whether patients are treated with vitamin K antagonists (VKA) or new (direct) anticoagulants (NOACs). In randomized controlled trials GIB rate was comparable or even higher in NOAC patients as compared to VKA. Prospective randomized trials among different NOACs are not yet available.

The present retrospective observation study included 830 patients with upper GIB (55.2%), GIB from colon and rectum (42.5%) and small bowel (0.8%) GIB treated in rural community care hospital in Meißen, Saxony between January 2012 and December 2014. Endoscopic treatment was applied in 21.8% cases, and only 2.6% patients underwent surgery. 24.2% patients received oral anticoagulant at the time of bleeding onset: 13.9% VKA and 10.4% NOACs. Antiplatelet drugs were common in the studied population (35.2%), whereas the combination of an oral anticoagulant and single or double antiplatelet therapy was with 1.9% or 0.8% rare. Patients receiving oral anticoagulation were older compared to naïve group (mean 77.8±9.0 and 70.9±16.2 years) and had more frequently comorbidities such as ischemic heart disease 29.9%, diabetes mellitus 36%, active malignant disease 14.9%. The rate of active bleeding on endoscopy and the need for endoscopic therapy was similar in groups on/off anticoagulation (7.5% and 10.5% respectively). Peptic lesions in upper GI tract were the most common bleeding sources in both groups (30% cases); there was no specific GIB pattern in patients on oral anticoagulation as compared to naïve.

Blood products including prothrombin complex concentrate (PCC) were transfused in 45.8% anticoagulated and 42.6% naïve patients, mean 1.8 and 1.6 units of packed red blood cells were used respectively. There was no difference in the length of stay in intensive care unit between naïve and anticoagulated patients (mean 6.1 and 6.5 days respectively).

6.6% recurrent GIB occurred during the same hospital stay and 3.3% more within – 30 days after the discharge, there was no association with oral anticoagulation prior to the first GIB event. Recurrent GIB was associated with very high mortality: 34.5% patients with recurrent GIB died, compared to 4.4% in patients with a single bleeding episode. Patients who were hospitalized for a comorbidity and developed GIB later had poorer prognosis with mortality rates of 21%. Severe renal function impairment at admission (GFR<30ml/h) was associated with higher mortality, 16.7% compared to 4.6% in those with GFR≥30ml/h. There was no difference among NOAC, VKA users or naïve patients. Outcomes in the NOAC group with GFR values lower than approved for respective medications, were comparable to the other NOAC patients regarding mortality, active bleeding on endoscopy, rebleeding rates and blood components transfusion.

The mortality rate was significantly lower in anticoagulated patients: 3.5% compared to 7.3% in the therapy naïve. GIB was the cause of death in 24.6% cases, followed by infections (20%) and malignant tumors (15.4%).

In summary, GIB therapy outcomes were comparable in patients on/off anticoagulation which is in line with previously published reports. The results suggest that both VKA and NOACs can be administered to multimorbid and elderly patients with comparable GIB risks for both substance classes.

Lower mortality in the anticoagulation group of the current study might be due to a selection bias: possibly these were fitter and low-risk patients who were prescribed OACs. This selection bias is very probable in the observational study and should be taken into account when interpreting the results.

3. Introduction

Gastrointestinal bleedings are common and life-threatening. Anticoagulation therapy increases bleeding risks, including GIB. In the real-life setting patients' surveillance and compliance is poorer, than in large randomized controlled trials, which must be also true for the NOAC-therapy. One of the first observational nation-wide studies comparing dabigatran and warfarin evoked concerns about the safety of the new anticoagulation substance [1, 2]. The other post-marketing studies in mixed rural and urban populations were more consistent with the randomized trials [3, 4]. The current study provides a piece of evidence from an individual rural hospital during the first years after NOACs introduction to the market.

4. Gastrointestinal bleeding

4.1.Epidemiology of GIB

Gastrointestinal bleeding is a frequent gastroenterological emergency with high morbidity and mortality, defined as upper GIB when proximal to ligament of Treitz and lower GIB when distal to ileocaecal valve, there is also a small intestinal bleeding occurring localized between these two anatomic landmarks [5, 6].

UGIB is by far more common in the general population, representing ≈80% of all GIB with an incidence of ≈150 per 100.000 inhabitants per year in the United States [5, 7], European population-based studies report varying data: 48/58/172 per 100.000 inhabitants per year [8-10], (Netherlands 2000/ Denmark 1991/ Scotland 1992), German data is 115 UGIB cases per 100.000 inhabitants per year in 2005 [11]. Surprisingly there are studies reporting an increasing frequency of LGIB compared to UGIB in special clinical settings and patients subgroups [12]. The variance in statistics is believed to be dependent on population properties and also definitions of UGIB in each study, such as inclusion or exclusion of not admitted outpatients or GIB developed during hospital stay admitted with bleeding non-related diagnoses [9]. Bleeding from the esophageal and gastric varices accounting for 5 to 40% of UGIB admissions varies widely depending on population involved and is often reported and studied separately due to a specific pathogenesis and significantly poorer outcomes. LGIB has an incidence of 20-36 per 100.000 persons per year (US data) [5].

GIB may account for up to one third of urgent admissions to the hospital [13]. In addition to patients with GIB referred to the hospital up to 1/3 of UGIB occur during hospital stay in patients admitted with bleeding non-related diagnoses, including ICU patients [5, 9]. These inpatients' GIBs represent a group with significant higher mortality, 11-40% [9, 14]. Proportion of inpatients among all LGIB is reported by 10% [15].

The rate of in-hospital mortality is stated as 2% to 4% for UGIB in the recent US reviews and monographies [5, 14] and 1.5% for LGIB [5]. At the same time individual population-based studies report mortality of 3.1-10% for UGIB [9, 16, 17] and 2.1-4% for LGIB [18, 19]. A prospective multicenter study from the two years, 1993 and 2000 reports a much higher and unchanged in-hospital mortality of 14-15% for UGIB [10]. Mortality rates stay high and close to unchanged in the last decade despite better control of the bleeding lesions and systemic therapy, an effect mostly explained by ageing of the population and rising burden of comorbidities [5, 9, 16]. Mortality is attributed largely due to decompensation of comorbidities, whereas fatal exsanguination is rare [5, 18, 20].

As the fatal events rate is relatively low and heterogeneous, it was suggested to use rebleeding rate as a reference outcome in studies of UGIB, given its definition is uniform [21]. Rebleeding has been shown to be an independent predictor for mortality in many studies of UGIB [14, 22]. At the same time no study reports a significant association between rebleeding from lower GI lesions and mortality, although it leads to higher resource utilization, longer hospital stay, and decreased quality of life [18].

Indeed, the rebleeding rate is rising with observation time, and a period of 30 days is widely accepted. There are reports of 14% and 4.9-7% of rebleeding events within 30 days for UGIB and LGIB respectively [16, 18, 19], dependent on specific etiology.

4.2.Diagnoses/bleeding lesions and their treatment

Patients with GIB present with either of the following symptoms or their combination: shock, hematemesis, vomiting with "coffee grounds" masses, epigastric pain, melena, maroon stools or hematochezia, or a combination of these. Another possible sign of a GIB is an iron deficiency anemia, decrease of hemoglobin which is more typical for a lesion with slow bleeding rate [5, 7].

4.2.1. Non-variceal upper GIB

Data for non-variceal UGIB is presented below in a table. The first column contains prospective observational data, collected in 1999-2002 in a large population-based Canadian study [16] with n=1861 patients, this study is representing a contemporary distribution of upper GIB lesions after the introduction of PPI-therapy and may be treated as reference study. Columns to the right depict frequency of bleeding lesions in patients receiving an oral anticoagulation - VKA only for studies from 2007 and 2011 and both VKA and NOACs in the 2014 study. Notably, data in the last column to the right comes from the study by Rubin et al. [23] with patients taking VKA and having supratherapeutic INR levels (INR>4) at the time of GIB.

		Only patients receiving OACs			Only INR>4
Study, Diagnosis, % of patients	Barkun, 2004 [16] n=1869	Wolf, 2007 [20] n=102 VKA only	Hearnshaw, 2011 [17] n=383 VKA only	Sengupta, 2014 [15] n=147 VKA and NOACs	Rubin, 2003 [23] n=37
Peptic ulcer, Σ esophageal	56 6 26	68	28	17 10	19

gastric duodenal	24			7	
Malignant tumor	-	-	3	-	-
Esophagitis	9	-	12	4	16
Erosive gastritis/duodenitis	10	-	28	10	46
Mallory-Weiss syndrome	-	9	4	2	3
Dieulafoy′s lesion	-	3	-	5	-
AVM	-	9	-	13	16
Other	25	11	3	1	-
Normal finding or Source not found	4.6		17	49	19

Table 1: Non-variceal UGIB lesions with and without OACs, data from selected studies (the sum may exceed 100% because of multiple bleeding lesions).

The most typical lesions in the upper GIT in the general population, as well as in the anticoagulated patients are peptic ulcerations and erosive gastritis/duodenitis.
The majority of UGIB is a result of imbalance in disruptive and protective factors, mainly of gastric acid effect and H.pylori infection on the mucosa of the esophagus, stomach and duodenum, combined with disturbed local repair mechanisms, drug effects and other factors.
Less lesions result from mechanical forces (including iatrogenic) which lead to mucosal and vascular damage: Mallory-Weiss syndrome, bleeding after polypectomy or papillotomy.
Vascular malformations (AVM) and Dieulafoy′s lesion present cases when relative mild damage to the mucosa could result in a massive blood loss, and a non-bleeding lesion could be easily overseen after spontaneous cessation of the bleeding. Malign tumor of the upper GIT with vessel arrosion, surface ulceration or necrosis is a rare cause of GIB, being associated with a very poor prognosis [5, 7].
Gastric and duodenal erosions without symptoms of GIB or dyspepsia are found in 5-15% of healthy individuals [24] and are not ultimately associated with developing of a GIB once the patient didn’t have signs or symptoms of a bleeding before endoscopy [5, 25].
The natural history of a non-variceal UGIB is so that most of the observed lesions (80-90%) are not bleeding at the moment of the endoscopy and often no further endoscopic intervention is

needed. However, part of these lesions will rebleed even after applied endoscopic and systemic therapy, raising the mortality among patients developing a recurrent upper GIB up to 10-fold [5]. Treatment of non-variceal UGIB is a combination of local and systemic therapies.

Local therapies are aimed at achieving haemostasis during an endoscopic session and preventing rebleeding. Mechanical therapies are broadly used: different modifications of clips and injection therapies (saline, adrenaline, fibrin tissue glue are most used). Thermal methods include mono- and bipolar electrocoagulation, thermocautery, non-contact argon plasma coagulation - a risk of a perforation when using these methods should be kept in mind. A combination of these modalities is applied in majority of cases [5, 26, 27]. Interventional radiology with endovascular treatment is utilized in centers having this expertise. Surgical treatment, mainly oversewing of the bleeding vessel or an organ resection is a rescue therapy which is reserved for patients bleeding even after repeated endoscopic treatment [5, 7, 28]. At least one attempt of endoscopic treatment is warranted for patients with recurrent bleeding before surgery is performed [29].

Medical treatment includes antisecretory drugs, mainstay of this therapy are intravenous or oral proton pump inhibitors, introduced in 1997 after a randomized controlled trial by Khuroo [30]. Other medications (e.g. octreotide) are of minor importance, whereas H2-antagonists haven't shown to decrease need for surgery and mortality and will not be discussed further [5, 31, 32].

Other medical therapies include fluid resuscitation and blood transfusion. An accent was recently made on benefits of restrictive blood transfusion strategy in patients with GIB leading to better outcomes [33]. Application of fresh frozen plasma/prothrombin complex concentrate is indicated in coagulopathy and in case of multiple packed red cells transfusion; transfusion of platelet concentrates is reserved for thrombocytopenia, and vitamin K application – for cases when oral anticoagulation with VKA [5, 34, 35]. Under special circumstances systemic anti-thrombolytic agents (aminocaproic acid and tranexamic acid) and prothrombotic (desmopressin) might be applied [36]. Antagonists of the NOACs, andexanet alfa and idarucizumab are the newly available treatment option for the respective group of patients [37, 38].

4.2.2. Variceal UGIB

Variceal bleedings represent a completely different patients' subpopulation, with portal hypertension and (in most cases) liver failure being driving factors for the bleeding event and mortality [5, 26, 39]. Patients with liver cirrhosis presenting with UGIB have nearly 50% prevalence of variceal bleeding. Esophageal and gastric fundal varices stop spontaneously only in 50% once they do bleed, and 10-20% of bleedings are poorly controllable by standard therapy leading to high mortality in these patients. Recurrence rate within the first 5-10 days is especially

high, reaching 50% to 70% within 6 weeks; mortality per each bleeding episode is estimated as 15-20%, though it has significantly reduced in the recent years [5, 39]. Complex therapy aimed at decreasing of portal hypertension and on mechanical cessation of bleeding is applied, accompanied by fluid resuscitation, antibiotics. Rescue therapies – TIPS, surgical shunt, balloon tamponade and liver transplantation are available options in cases of therapy failure [5, 26, 39]. Until recently, liver cirrhosis was considered to be a hypocoagulant state because reduction of platelets count and prolonged prothrombin time are commonly observed. This paradigm has been changed since a reduction in anticoagulant factors (AT III, Protein C, S) was also often observed [5, 39, 40]. Rate of thrombotic events in cirrhotic patients is higher than in the general population, with portal venous thrombosis prevalence of 10-25% [41] or 16% yearly [39, 40] in advanced liver disease. Treatment with anticoagulants has been shown to be effective in vessel recanalization leading to increased prescription of anticoagulants to these patients in the recent years.

4.2.3. Lower GIB

The most typical lesions in the lower GIT are presented below in a table. As in the UGIB summary, two left columns represent observational data of unselected patients. Columns to the right depict frequency of bleeding lesions in patients receiving OACs. The last column is data in the setting of supratherapeutic anticoagulation (INR>4).

			Only patients receiving OACs	Only INR>4
Study, Diagnosis, % of patients	Sengupta, 2015 [42], n=271	Aoki, 2015 [18] n=342	Sengupta, 2014 [15], n=50 VKA and NOACs	Rubin, 2003 [23] n=21*
Colonic diverticulum	18	50	32	10
AVM	3	2	-	10
Colonic and rectal polyp	-	-	-	5
Colorectal cancer	-	9	-	0
Colitis, Σ infectious nonspecific	21 3 18	11 5 6	12	5
Ischemic colitis	7	13	6	-

Ulcer	0	3	10	-
Hemorrhoids	8	4	12	5
Postpolypectomy bleeding	8	2	16	0
Radiation proctitis	3	1	12	-
Other	2	3	-	-
Normal finding or Source not found	30	3	-	43

Table 2: LGIB lesions with and without OACs, data from selected studies (frequency of findings is cited from original articles and doesn't make 100% when summed).

The most frequent lesions in the lower GIT leading to hospital admission are bleeding colonic diverticula [19]. Diverticulosis is a common finding in the colonoscopy, more often in the left colon, however the bleeding source is diagnosed mostly in colon ascendens for reasons not fully understood [5, 18, 19, 35]. Ischemic colitis and hemorrhoids were the most common detected LGIB source among in-hospital patients in one prospective study, each found in 20% of patients [42]. Most of the LGIB cease spontaneously and detection of the exact source may be not possible, so a diverticular bleeding is often proclaimed as a presumed diagnosis, when other bleeding sources are excluded and non-bleeding diverticula are seen. A shorter time to endoscopic evaluation (urgent colonoscopy defined as performed within 12-24 hours after hospital admission [43]) is shown to be safe but not leading to a higher yield of bleeding lesions [35, 44]. Factors associated with diverticular bleeding are alcohol consume, smoking, consume of NSAIDs, ASA and non-ASA antiplatelet drugs [19]. Lower GIB show high recurrence rate 10.4-19% within 1 year, with no ultimate prophylactic treatment available [18, 45, 46]. Higher comorbidity and advanced age was associated with higher readmission for rebleeding for lower GIB [18]. Notably, rebleeding episodes didn't have an association with mortality as shown for upper GIB [18, 19]. Both VKA and NOAC therapy was associated with higher mortality rates (2 of 21 cases due to bleeding) and recurrent bleeding episodes in an observational study [42]. Endoscopic treatment of LGIB consists of local treatment of bleeding vascular lesions similar to the upper GIT, once these lesions are presumed to be the bleeding source; clipping or injection therapy is appropriate for diverticular or postpolypectomy bleeding. Polypectomy or surgery for larger lesions is the definitive treatment for actively bleeding tumors or those postulated as the

bleeding source. Colitis, including inflammatory bowel disease, demands a combination of systemic and local treatment in most cases. A rare lesion - radiation colitis is treated most often locally [5, 35, 47]. Hemorrhoidal bleeding is treated with topical medications and ligation/sclerosant injection; surgery is indicated in some cases [35]. A gross surgical procedure (hemicolectomy, colectomy) is reserved for rare cases (4.4%) of persistent bleeding by colitis, diverticular bleeding, and ischemic colitis [42].

Probably, presented proportion of LGIB lesions in hospital-based clinical trials is disturbed by the fact, that minor and self-limited LGIB, precisely "outlet-type bleeding" due to hemorrhoids or anal fissures often go underreported or treated by general practitioners with diet recommendations or simply reassurance after proper anamnesis and physical examination including inspection of anal area [5, 35]. These minor bleedings play a significant role in the GIB statistic in prospective NOAC-trials, since they form the group of "minor bleedings" – a clinical presentation rarely seen and treated by ward physicians and hence underrepresented in most of the medical record-based trials, where data from participating hospitals is analyzed [9].

5. Anticoagulation drugs

Thromboembolic disorders are a major reason of morbidity and mortality. Building of thrombus can occur both in arteries and veins. Arterial thrombosis happens typically after rupture of an atherosclerotic plaque with building of a platelet-rich white thrombus. Typical clinical presentations are myocardial infarction, ischemic stroke, limb ischemia. Venous thrombosis originates in valve cups of the deep veins with a cascade of coagulation and results in building of an erythrocyte- and fibrin-rich red thrombus. Typical presentations are deep vein thrombosis, postthrombotic syndrome, and pulmonary embolism. In atrial fibrillation patients a venous-type thrombus forms most often in the left atrium appendage leading to clinical presentations similar to arterial thromboembolism. Major strategies to attenuate thromboembolic risks are administration of antiplatelet drugs (also in combination with anticoagulants) for arterial focus and administration of anticoagulants for venous focus [7].

In this focused review, heparins, parenteral direct thrombin inhibitors and fibrinolytic agents are not enlightened.

5.1. Vitamin K Antagonists

Substances leading to symptoms similar to vitamin K deficiency are known since 1954, with phenprocoumon being more used in Europe, and warfarin – in the US. VKAs are oral anticoagulants, drugs decreasing amount of biologically active clotting factors II (thrombin), VII, IX, X and also anticoagulant proteins C and S. VKA inhibit the γ-carboxylation of these

proteins, leading to their reduced or absent activity. Delay in the onset of VKA action depends on amount of readily circulating clotting factors with half-life times of 24-72h, so VKA therapy is complemented with another anticoagulant, typically heparin/LMWH, during the first 5 days of treatment [7].

VKAs have a very narrow therapeutic window, so they should be regularly controlled by measuring prothrombin time/INR. Therapeutic INR range for most conditions is 2.0 to 3.0. There are exceptions such as a mechanical heart valve in mitral position and other implanted prosthetic devices, when target INR range might be set higher, e.g. 2,5-3,5. VKAs have multiple drug and food interactions, so a routine monitoring of INR is needed for the whole duration of treatment [7].

It was shown, that in patients with excellent INR control stoke risk could be reduced to 80-85% compared to 66% risk reduction in standard treatment regimens [48]. In the ACTIVE W trial focused on prophylaxis of thromboembolism in AF patients, warfarin was superior to double antiplatelet therapy with ASA and clopidogrel only when the time in therapeutic INR range was over 65%, as reviewed by Ruff et al [49].

There were no significant differences shown in direct or side effects between different vitamin K antagonists (warfarin, phenprocoumon) in a large retrospective study [8].

Action of VKAs can be reversed by withdrawing of respective medications (it takes 3 to over 7 days until haemostasis normalization), or in acute setting by applying Vitamin K orally/parenterally; a fall of INR is present in few hours in most cases [50, 51]. Fresh frozen plasma or more effective: prothrombin complex concentrate (PCC) is a rescue-therapy with rapid onset of effect, which is reserved for patients with life-threatening bleeding or need for urgent surgery [5, 51].

5.2.Non-vitamin K antagonist oral anticoagulants (NOACs)

Oral direct thrombin inhibitor dabigatran (Pradaxa®) and factor Xa inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Lixiana®) are recently available alternatives to VKAs. They are administered orally and have a rapid onset and offset of action, with predictable pharmacokinetics and pharmacodynamics.

NOACs are given in fixed doses once or twice daily and need no routine efficacy monitoring. INR is elevated in use of rivaroxaban (and less for apixaban), and aPTT is prolonged in use of dabigatran, although these laboratory changes are very dependent on time of the last drug intake. Dilute thrombin clotting time and anti-factor Xa assays are appropriate for drug efficacy

monitoring in dabigatran and Xa-inhibitors respectively, although their utilization in real-life setting is very rare [7, 50].

A summary of OAC and NOAC properties is presented in a table below.

Characteristic	Phenprocoumon	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Physiological action target	Vitamin K epoxide reductase	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Bioavailability	99%	6%	80%	60%	50%
Dosing	Dependent on INR	BID	QD or BID dependent on indication	BID	QD
Half-life time	160h	12-17h	7-11h	12h	9-11h
Renal excretion	No	80%	33%	25%	35%
Means of monitoring	INR	No	No	No	No
In European market since	(1950-s)	2011	2009	2011	2015

Table 3: Summary of VKA and NOAC pharmacological properties.

5.2.1. NOAC Pharmacokinetics and pharmacodynamics

Once taken orally, the NOACs show their maximum effect in approx. 2 hours. Xa antagonists circulate in serum protein-bound whereas dabigatran could be dialyzed. Elimination through renal and hepatic pathway has different proportions for each drug [50].

Notably, dabigatran etexilate is a prodrug, which is absorbed only to 6% in the GI tract and is converted to active form by esterases in serum. It was however shown, that stools don't contain a prodrug, but only the active drug; it is believed the bacterial esterases play an important role in this transition [24, 48]. The factor Xa antagonists are shown to form a higher local concentration in the GIT when given once daily compared to twice daily regimen (e.g. rivaroxaban vs. apixaban) [48]. These pharmacokinetic feature is believed to play a role in the pathogenesis of lower GIB in patients receiving any of the NOACs [24].

Severe renal insufficiency was initially a contraindication for the NOACs, and a dose reduction is recommended in patients with GFR under 50/min. Low-dose apixaban, edoxaban, rivaroxaban

are approved for patients with GFR 15-30 ml/min and dabigatran only in GFR over 30ml/min [50]. Guidelines do not recommend application of NOACs in patients on hemodialysis [52]. There is a drug cumulation effect measured by anti-Xa-activity described for patients receiving apixaban and developing an acute renal failure [53]. At the same time, a large retrospective study of off-label use of apixaban in patients in chronic hemodialysis showed similar or lower rates of major bleeding complications when matched against warfarin users [54].

5.2.2. NOACs Therapeutic effects

The pharmacologic efficacy of all 4 NOACs for preventing stroke in patients with non-valvular AF was studied in Phase 3 randomized controlled clinical trials compared with warfarin [55-58]. In all RCTs a non-inferiority (rivaroxaban, edoxaban) and even superiority (apixaban, dabigatran) relative to stroke prevention was shown. Main benefit of therapy with NOACs was a protection against hemorrhagic stroke (reduction approximately to 50%); at the same time protection against ischemic stroke was comparable to warfarin. The meta-analysis of these studies has shown a 10% reduction in mortality compared to warfarin [49].
Further studies were undertaken in clinical setting of pulmonary embolism, acute coronary syndrome and deep vein thrombosis leading to licensing of NOACs for these indications; perioperative application of NOACs was approved for VTE prophylaxis in elective orthopedic surgery. Two RCT of prophylactic apixaban and rivaroxaban in selected outpatient cancer patients receiving chemotherapy yielded promising results relative to reduction of VTE events although rate of bleeding complications was considerably high [59, 60]. A study of prolonged apixaban use for VTE prophylaxis in patients with congestive heart failure yielded negative results and resulted in increased major bleeding complications [61].
Therapeutic effect of NOACs is irrespective of prior treatment with conventional VKA-anticoagulants, there was no difference between so called “naïve” and “experienced” patients [49]. There was also no rebound effect after withdrawing of NOACs as shown in the rivaroxaban trial ROCKET-AF: frequency of thromboembolic events was similar during the first month and one year after therapy discontinuation [58].

5.2.3. (N)OACs Side effects

Spectrum of side effects of both VKA and all of the NOACs differed minimally among substances and was dose-dependent in the pivotal NOAC trials [55-58]. There is an ultimately accepted HAS-BLED Score used to assess o estimate the 1-year risk for major bleeding [62]. Major concerns in anticoagulant drugs are bleeding events (GIB will be discussed in Chapter 6 of this review). A most life-threatening and disabling, intracranial bleeding (including

hemorrhagic stroke) was lower in all compared drug regimens [49]. The reason for this difference is not clear identified, and more addressed effect of NOACs on one clotting factor compared to pleiotropic effect of VKA is suggested. It has been shown that most ICB occur within therapeutic range of INR, so a rigorous INR monitoring is not expected to a further risk reduction. At the same time, NOACs have less adverse effects than VKA also in centers with well-controlled INR and by far - in centers with poor INR control [48].

There was an increased concern about the high level of reported lethal bleeding complications in the early post-marketing phase of dabigatran, but a thorough FDA investigation didn't confirm any additional risks compared to warfarin [2].

Dyspepsia is a frequently described side effect of dabigatran (but not factor Xa-antagonists), leading to discontinuation of therapy in a significant number of patients as reviewed by Chang et al [63]. In the RE-LY trial dyspepsia was registered in 11.3%-11.8% of patients (compared to 5.8% in the warfarin group), in the RE-COVER study dyspepsia rate was lower, 2.9% in dabigatran group vs. 0.9% for warfarin users, and this side effect wasn't reported as leading to therapy discontinuation in neither of the two studies [55, 64].

Switching from warfarin to dabigatran was addressed in a robust US Veterans Affairs retrospective registry-study (n=85,334) and was associated with slight increase of GIB within following 15 months, weighted odds ratio was 1.54; there was no significant association with other bleeding events compared to continued warfarin [65]. In a prospective observational cohort in Dresden, bleeding and cardiovascular events rate during the therapy switch from VKA to dabigatran or rivaroxaban was observed in n=546 patients, with rate of major bleeding events of 0.3%/30 days [66].

5.2.4. Antidotes for NOACs

Andexanet alfa is a recombinant human factor Xa decoy protein. A trial of its activity in binding rivaroxaban/apixaban in healthy elderly volunteers was published in 2015 showing a rapid effect onset after a single bolus and remaining for the time of infusion (rivaroxaban and apixaban are bound to plasma proteins). No major adverse events were reported [38].

Idarucizumab is an antibody fragment against dabigatran tested in a clinical setting of serious bleeding or an urgent surgery. It has shown a rapid onset of action within minutes after application, its effect lasted for 24 hours [37].

6. Gastrointestinal bleeding in patients receiving antithrombotic therapy

GIB are not the only bleeding events occurring in patients under antithrombotic therapy. Operation site and traumatic/spontaneous hematomas, post-puncture bleeding from solid organ

and vessels, into pericardium, intra-articular, retroperitoneal, urinary tract bleeding, epistaxis and hemoptysis are described. Nevertheless, GIB are second most clinically significant after the ICB and put patients at a higher risk of death. In population-based reports, the rate of bleeding sources other than ICB and GIB was 62%, whereas 30-day mortality after ICB was approaching 50% compared to 5% for extra-cranial bleeding [67, 68].

6.1.Effect of antiplatelet drugs: aspirin and P2Y12 antagonists.

Used since 1899, aspirin even in low doses (75-325 mg) is shown to increase the risk of erosions in the upper GIT [69] and also in small bowel [70] even in otherwise healthy volunteers. Consequently, the rate of GIB in ASA-treated patients is doubled compared to placebo, although absolute increase in incidence rate stays low in unselected population by 0.12% yearly, and 0.23% yearly in other observational studies [5, 69]. For comparison, basal GIB rate without risk factors or medications is 0.06% as observed in general population and 0.3-0.5% in patients with AF [24]. Effect of ASA on upper and lower GIB is supposed to be equal, although mechanism of mucosal damage in small bowel and lower GIT is much less understood [45]. It is shown, that no formulation of ASA (buffered, enteric-coated, etc.) and even the smallest effective dosage could not make it safe for GIT mucosa [69].

Non-ASA antiplatelet drugs, adenosine diphosphate receptor P2Y12 antagonists clopidogrel, ticagrelor and prasugrel are also shown to elevate the risk of GIB although a direct mucosal effect isn't described [71]. GIB risk elevation is more prominent in combination of ASA with the 3d generation P2Y12 antagonists ticagrelor and prasugrel than in ASA + clopidogrel. Any combination of double antiplatelet therapy yields more risks than ASA-monotherapy [71, 72]. Data on direct head-to-head risk comparison for a GIB between ASA and clopidogrel is sparse. There is a consensus that clopidogrel itself doesn't evoke new GIT mucosal lesions [71]. In a meta-analysis addressing GIB risks with ASA versus clopidogrel a minimal increase of GIB rate in ASA group was absolute annual increase was 0.12%, with number needed to harm calculated to be 769 patients [73]. Trials comparing ASA + PPI with clopidogrel alone report better outcomes for ASA + PPI group, and this combination is preferred over clopidogrel alone to reduce rebleeding [22]. Further publications recommend ASA + PPI in high-risk patients with peptic ulcer anamnesis when antiplatelet therapy is required for secondary prophylaxis; ASA should be avoided in these patients for primary prophylaxis. The main stress is made on the undoubtedly higher risk burden in case of a double antiplatelet therapy [5, 22, 72, 74, 75]. Combination of ASA and other antiplatelet drugs, also called double antiplatelet therapy increases the risk of upper GIB to 2-5.5 times in non-selected population, compared to ASA

alone [5, 76]. In a study of patients after percutaneous coronary intervention risk of GIB under double antiplatelet therapy was significantly increased, with unexpectedly higher rate of LGIB than UGIB [12]. Risk of recurrent LGIB is higher in case of double antiplatelet therapy, than in monotherapy, and in both cases significantly higher than in naïve patients [18].

6.2.Effect of NOACs on GIB risk

Neither VKA nor the NOACs have been proven to cause a mucosal damage itself [71]. At the same time, they can precipitate a clinically relevant or obscure GIB from a prior asymptomatic lesion throughout the GIT, reflecting the spectrum of pathologies seen in the population [24]. Combined with other drugs with established potential for mucosal damage, risk of GIB would further increase.

VKAs are well-known drugs serving as comparators in modern studies of NOACs, so NOACs effect will be reviewed in this context. In the 4 pivotal phase III studies of NOACs comparing outcomes in patients with non-valvular AF, rates of major bleedings was non-superior for dabigatran and rivaroxaban [55, 58] or lower for apixaban, edoxaban [56, 57]. At the same time rates of GIB were dose-dependent: in high-dose dabigatran and high-dose edoxaban - higher, in low-dose edoxaban lower and in other regimens similar to that in warfarin group.

	Study treatment [55-58]					
Outcome vs. warfarin	Dabigatran 150mg BID	Dabigatran 110mg BID	Apixaban 5mg BID	Rivaroxaban 20mg QD	Edoxaban 30mg QD	Edoxaban 60mg QD
Stroke Σ, % per year	1.11 vs. 1.69 *	1.53 vs. 1.69	1.27 vs. 1.60 *	1.7 vs. 2.2	1.91 vs. 1.69	1.49 vs. 1.69
Major bleeding, % per year	3.11 vs. 3.36	2.71 vs. 3.36 *	2.13 vs. 3.09 *	3.6 vs. 3.4	1.61 vs. 3.43 *	2.75 vs. 3.43 *
Major GIB, % per year	1.51 vs. 1.02 *	1.12 vs. 1.02	0.76 vs. 0.86	3.2 vs. 2.2	0.82 vs. 1.23 *	1.51 vs. 1.23 *
Mortality, % per year	3.64 vs. 4.13	3.75 vs. 4.13	3.52 vs. 3.94 *	1.9 vs. 2.2	3.80 vs. 4.35 *	3.99 vs. 4.35

Table 4: Major outcomes of the pivotal NOAC trails in AF patients. * highlighted by grey background indicates statistically significant difference compared to VKA

Although the study populations were not identical relative to age and comorbidities, several meta-analyses were performed. One analysis including 43 randomized controlled trials comparing NOACs with standard care (warfarin, heparin, LMWH) has shown an odds ratio (OR) for GIB of 1.45 (95% CI 1.07-1.97) although with a high level of heterogeneity. Risk elevation was more prominent in patient subgroups with venous thrombosis (OR 1.59), acute coronary syndrome (OR 5.21, here most probably because additional of single/double antiplatelet therapy applied). Risk elevation was also higher for patients receiving dabigatran (OR 1.58) and rivaroxaban (OR 1.48) compared to other NOACs, standard care and other clinical settings [77]. It was a matter of concern, that the rate of GIB in the pivotal dabigatran RE-LY study was significantly higher in the group with 150mg dabigatran twice daily compared to warfarin (relative risk 1.50) [55]. A robust post-marketing population-based trial with over 15,000 patients receiving dabigatran and warfarin was performed in Denmark (also referred to as "Danish cohort"). One of the study results was a lower, compared to the phase III dabigatran study, GIB rate, not different from the warfarin study arm [1]. Further retrospective register-based US studies report similar rates of bleeding complications among warfarin, rivaroxaban, and dabigatran users [2, 63, 78].

In an observational cohort, often referred to as "Dresden NOAC registry", over 2,500 patients taking NOACs rivaroxaban and dabigatran were prospectively enrolled with efficacy and safety outcomes registered, these were comparable with the respective phase 3 RCTs [3, 4]. According to this cohort study, only 3% to 6% of all bleeding events among patients taking NOAC were major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) definition, no subdivision in GIB and other sources was provided. Incidence of major bleeding was 1.7, 1.9, 3.1 per 100 patient-years (dabigatran 150mg, 110mg BID and rivaroxaban respectively). These bleeding rates were comparable with those from randomized controlled trials, confirming safety of these medications now on daily-care setting. This is a special concern because rate of OAC-associated bleedings was much higher once studied in daily-care settings compared to clinical trials, where a better surveillance was provided [51, 79].

NOAC-treated patients in a community practice setting included in the modern Dresdner cohort study [4] have shown better safety outcomes compared to observations in an VKA-treated cohort in the same geographical area in 2005 [68]: 90-day mortality was lower (6.3% vs. 14.1%). Favorable safety outcomes in the NOAC cohort are also seen when compared to other daily-care OAC-treated cohorts where overall mortality rates up to 8%, and mortality in hospitalized patients 13-18% were reported, as summarized by Dr. Beyer-Westendorf [4].

6.3.Effect of complex antithrombotic therapy and other medications

Patients with complex antithrombotic therapy are often excluded from studies [80], as explicitly documented in the pivotal apixaban trial [57].

Combination of ASA or NSAIDs with warfarin increases GIB risk approximately twice compared to warfarin alone [24, 73]. Multiple drug combinations were analyzed relative to association with upper GIB in a large European database-study; a maximum risk was associated with the use of NSAID and steroids (incidence rate ratio 12.8); OAC+NSAID and OAC+ASA yielded incidence rate ratio 8.7 and 6.9 respectively [76]. However in a large retrospective database-study of upper and lower GI bleedings [80] a combination of OAC and antiplatelets increased GIB risk to a smaller extent than in the aforementioned report (hazard ratio 1.6). As with all registry-based studies, many factors including selection bias and undetected over-the-counter NSAIDs could have confounded the results.

Aldosterone antagonists and SSRIs in addition to more acknowledged risk factors such as selective COX-2 inhibitors and steroids put patients at increased risk of GIB, when prescribed alone or in combinations [76].

6.4.Risk factors for rebleeding and mortality in patients with GIB receiving VKA/NOAC

Peptic ulcer disease, use of NSAIDs and H. pylori infection are risk factors for GIB known since 1980-s/90-s. Later the NSAID-, ASA- and anticoagulant-induced small- and large bowel lesions were recognized although a clear pathogenetic sequelae of a LGIB in this setting is not yet defined [72]. Comorbidity, but not age, is an independent risk factor for poor outcomes in patients with GIB as proved in many trials [8, 14, 81].

Presence of anticoagulation with VKA at the moment of UGIB was shown not to be associated with a higher rate of rebleeding, mortality or surgery [20]. In that 2007 study by Wolf et al. some discrepancies such as high rate of spontaneous restoration of INR (without registered vitamin K application) and delayed endoscopic evaluation (median time: 72h) should be noted.

Presence of OACs alone could not be shown as independent factor associated with mortality after GIB in 2 retrospective community-based cohorts, although a selection bias is very probable, when only fitter and low-risk patients actually received the study medication (VKA) [82].

Even supratherapeutic levels of INR at the time of presentation (compared to patients with INR values 2.0-3.9) in patients on VKA treatment was not associated with higher rate of treatable lesions on endoscopy, need for transfusions, length of hospital stay, or mortality [23].

In a review by N. Abraham [72], following risk factors for GIB under complex antithrombotic therapy were formulated: prior history of GIB and peptic ulcer disease, advanced age, high level

of comorbidity, concomitant use of 2 antiplatelet drugs, NSAIDs and OAC. Possibly, patients with ASA-associated dyspepsia, users of oral glucocorticoids and males are also at higher risk.
A retrospective British study of patients undergoing surgery or transcatheter arterial embolization for recurrent non-variceal UGIB where endoscopic treatment had failed, revealed coagulopathy (defined as INR>1.5 by authors) as the most powerful predictor of endoscopic therapy failure [28].
UGIB in cirrhotic patients treated with anticoagulants was analyzed in a retrospective manner (2005-2012) with a contra-intuitive result of non-inferior outcomes relative to uncontrolled bleeding and mortality in patients receiving anticoagulation compared to therapy-naïve controls [40]. Furthermore, reported treatment failure rate and 6-week mortality were comparable with other studies of variceal UGIB. Authors suggest that the variceal bleeding itself is becoming a (locally) controllable condition, but the extent of liver disease and comorbidities are responsible for mortality rates. Authors also postulate that the anticoagulation *per se* has not to date been proved to be a factor increasing the risk of variceal GIB, supporting this with retrospective trials data. As to date, this thesis hasn't been tested in a prospective trial.
In contrast to UGIB, patients with LGIB who have OACs at hospital discharge are at higher risk of GIB recurrence and readmission [42], and mortality is higher in these patients according to another study [18]. There is also a sound base of evidence, that use of antiplatelet drugs (both ASA and non-ASA) and NSAID are independent and important risk factors for LGIB recurrence [18, 19, 42].

6.5.Changing GIB epidemiology

LGIBs associated with chronic NSAID therapy are becoming even more frequent than UGIBs according to many clinical reports; patients with LGIB require more resources, mortality and length of hospital stay is higher [12, 45, 46, 72]. There is an increasing trend in incidence of LGIB according to some population-based studies and reviews [45, 72] which is however not yet reflected in contemporary textbooks and guidelines [5, 7, 31, 35]. The prior 80% UGIB/20% LGIB proportion is further converging when patients under antithrombotic treatment are in focus [56, 68, 72, 82], there are studies reporting even a higher incidence of LGIB over UGIB, 3.5:1 [80], 3:1 [12].
Availability and proper implication of preventive strategies for UGIB prophylaxis (PPI, H. pylori eradication) together with lacking effective LGIB prophylaxis concept may explain relative increase in LGIB rates. At the same time population ageing, high rate of comorbidities, (N)OAC,

ASA- and antiplatelet agents' prescription and need for NSAID may lead to increase of absolute LGIB incidence [12, 45, 72].

6.6.Treatment of GIB in patients under (N)OAC treatment

A GIB in a patient receiving OACs doesn't present new pathologic lesions in the GIT and a timely endoscopic evaluation is indicated in all patients since many of them will need local treatment that would improve the outcomes. Initial medical treatment should be guided by clinical situation, with balanced fluid resuscitation to avoid heart failure [42] and packed erythrocytes transfusion when appropriate [33].

Temporary suspension of NOACs is justified in patients with acute GIB [5, 43]. Time is the most important antidote for NOACs as half-lives of most substances is approximately 12h in patients with sufficient renal function. On the other side, time needed for correction of haemostasis should not delay the endoscopic evaluation [29, 43].

The Guideline of American College of Gastroenterology recommends treating the supratherapeutic anticoagulation, since this may facilitate the endoscopic treatment [29], German Society for Digestive and Metabolic Diseases recommends antagonizing the anticoagulation treatment before endoscopy only in cases of severe GIB or in cases of failed endoscopic treatment [43].

Attempts to reduce the degree of anticoagulation with means of dialysis are minimally described for dabigatran and dialysis is not appropriate for protein-bound factor Xa inhibitors. Antidotes andexanet and idarucizumab have been tested in clinical trials showing high efficacy and safety, but their role in the routine treatment of GIB is not clearly defined yet [37, 38, 43]. PCC may be reserved for life-threatening bleedings although its efficacy is not firmly established. Transfusion of FFPs is less effective compared to PCC in restoration of coagulopathy in NOAC-treated patients, but FFPs keep their role as a component of transfusion strategy. Use of procoagulants (tranexamic acid et al.), vitamin K or protamine is of no use in NOAC-treated patients [50].

It is emphasized, that an early reinstitution of antithrombotic therapy – antiplatelet agents or anticoagulants - is important once the haemostasis is sufficient. As shown in ASA-treated patients undergoing endoscopic treatment for peptic ulcer bleeding, an early restart of antiplatelet therapy leads to less cardiovascular events and doesn't increase rebleeding rates; however there were no OACs in that study [83]. Notably, due to pharmacologic properties, ASA effect lasts approximately 5 days after therapy cessation. Most rebleeding in this trial happened on days 3 to 5, whereas majority cardiovascular complications occurred later than 5 days after the bleeding and ASA suspension.

There is no hard evidence or prospective trials addressing resuming of anticoagulation in patients with GIB. Expert societies recommend to weight risk of bleeding against risk of thrombotic events, a multidisciplinary approach to the patient is encouraged [43]. Danish society of Gastroenterology and Hepatology guidelines recommend restarting ASA 24h after there is no sign of bleeding, P2Y12 inhibitors could be restarted on the 3d day, SSRI on 5th day [75]. According to perioperative NOAC management guidelines, anticoagulation could be started 72 hours after an operation [50], this recommendation may be extrapolated on GIB patients.
In a prospective observational study by N. Sengupta, resuming of both oral and parenteral anticoagulation in patients with GIB was not associated with higher rate of rebleeding within 30 days, but suspending OACs for longer time resulted in significantly more thromboembolism; active malignancy was proven to be an independent risk factor for VTE events [15]. Authors thus suggest resuming anticoagulation within 2 weeks from the bleeding event.
The study of rivaroxaban, ROCKET-AF gives an insight into how high the rate of VTE events in atrial fibrillation patients discontinuing anticoagulation could be: a yearly 4.3-4.7% stroke risk was observed in patients discontinuing trial medication and not receiving conventional VKA[58].

7. Study design

A retrospective monocentric cohort study of patients with GIB was performed in a rural hospital in Meissen. Patients under therapy with VKA and NOACs were the special focus of this study.

8. Patients, materials and methods

8.1.Study material

The Elblandklinikum Meissen is a regional hospital in a Saxony district´s capital with 30,000 citizens, whereas a total of 245,000 inhabitants are treated in 5 acute hospitals in the region. 3 hospitals including the current one which is located geographically between the other two are bound in a cooperation network with a common patients' database (Orbis™, Agfa Healthcare). All patients, treated for a GIB in the clinic between 01.2012 and 12.2014 were analyzed. The study collective consisted of gastroenterologic, cardiologic and also surgical, orthopedic, neurologic and ICU patients. The initial search was performed based on the list of ordered endoscopic studies on each day of the time period. Further information was found in the electronic medical record.
The study database was created precisely for this trial using Microsoft Excel™. A single study case was defined as a hospital stay of an individual patient, with recurrent hospitalizations

registered as multiple cases, whereas recurrent bleeding within the same hospital stay were treated as the same clinical case. Recurrent hospitalizations were analyzed separately.

8.2.Study protocol

Inclusion criteria	Exclusion criteria
Application for an endoscopic study	No documented GIB signs or symptoms, either acute or chronic
Documented acute GIB event with fresh or metabolized blood in stools/emesis OR other relevant symptoms and signs, then WITH at least one of the following: a) fresh blood in the GIT or bleeding stigmata during the endoscopy OR b) performed endoscopic treatment OR c) reduction of hemoglobin by 1.2 mmol/l OR d) transfusion of RBC units	A “multifactorial anemia” documented in the clinical record (even with packed RBC transfusion) WITHOUT relevant endoscopic and/or clinical findings
	Positive test for occult blood in stool WITHOUT relevant endoscopic and/or clinical findings

Table 5: Study design, inclusion and exclusion criteria.

The following procedure was used during screening of hospital database for eligible patients:

0. All patients applied for an endoscopic study were critically evaluated based on their complete medical record. Only few patients were applied for an endoscopy and it wasn’t performed, in this case the presence of a bleeding event was judged based on the complete medical record.
1. Once there was a normal endoscopic finding and no bleeding signs/symptoms mentioned in the medical record, the case was excluded (that was the case in >75% of endoscopies).
2. A patient was included in the study when he/she had an explicit GIB with blood seen in stools/emesis or during the endoscopy. A validation of the bleeding signs by the referring

physician, OR a nurse, OR a hospital physician was required. In this case even a normal endoscopic finding could not lead to case exclusion.

3. Once the endoscopy provided a possible bleeding source and the patient had relevant symptoms/signs of a GIB, that case was included. A hemoglobin reduction of 1.2 mmol/l or need for RBC transfusion was counted as a sign of blood loss. Every case requiring endoscopic therapy was also included.
4. Cases of anemia without clinic and endoscopic signs of a GIB were excluded even if RBC transfusion took place. Several cases with postulated or assumed GIB in the medical record were excluded from the study, since the requirements 2. or 3. were not met.
5. Patients with solely positive fecal blood test were also excluded, if the endoscopic studies and clinical evaluation failed to provide an explanation for the finding.

The broadly utilized and objective ISTH criteria [84] for standardizing the reporting of bleeding symptoms in clinical trials were not applicable, since all the patients were readily in hospital for their bleeding and endoscopy was the inclusion criteria for the current study.

8.3.Groups definition

Patients receiving OACs were of special interest in this study. A patient was sorted to group "OAC", consisting of Vitamin K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOAC) when he/she was receiving the medication to the moment of bleeding begin, whereas patients receiving heparins as "bridging" with suspended VKA/NOAC were treated as OAC-naïve. Patients receiving apixaban, dabigatran, rivaroxaban were stratified according to their treatment respectively. Indication and dosage of the NOACs was documented.

8.4.Study methods

The main source of the patient data was the electronic medical record, including the endoscopy protocol. Information about hospital treatment before and in many cases after the respective endoscopy time was readily available from three neighboring clinics, offering a more detailed view into the disease progression, comorbidities and reducing the amount of incomplete data and rate of "lost to follow up".

There was no data on prescribed outpatient treatment, except documented in the past medical history field.

Basic demographic and statistical data was collected: name, sex, date of birth, date of endoscopy, urgent or elective timing of the study (defined as emergency/urgent by the endoscopist), number of days from hospitalization to endoscopy and then to discharge, and days in the intensive care

unit. Presentation with shock was defined if at least one of three criteria was fulfilled: tachycardia (pulse 100 beats/min), hypotension (systolic BP <100 mmHg) or syncope.
Both elective and urgent endoscopic studies in the Elblandklinikum were completed by trained physicians with at least one Facharzt-qualified colleague present during the study.
Localization and diagnosis that resulted in bleeding was carefully documented. Histological studies, if applied, were reviewed, Helicobacter pylori status was registered.
Cases with multiple bleeding sources were documented. If an uncertainty about the bleeding source was stated by the ward physician or the endoscopist, a special remark was made in the database.
The type of endoscopic treatment and rebleeding episodes, as well as rescue therapy (surgery, intravascular interventions, etc.) were documented when present. Data on endoscopic complications was searched in the protocols and in the medical record.
Transfusion of RBC, FFP, PC and PCC was documented based on clinical records and laboratory documentation. Data on Vitamin K application was intentionally not analyzed because of scarce documentation. Antagonists of NOACs were not yet approved for use in the time period analyzed.
A complex evaluation was needed in cases of bleedings, developed in patients admitted with bleeding non-related diagnoses. The diagnosis leading to the respective hospitalization was documented.
In cases of fatal outcomes, the cause was documented according to the medical record. Statistics of readmissions or rebleeding within 30 days of discharge and death 30 days after endoscopy was documented.
Data on prior GIB and GIB recurrence till the end of the study period was collected.
Indication, substance name and dosage of the OAC were registered if appropriate.
Comorbidities were registered as stated in the record to the moment of the bleeding. There was a potential bias in determining the specter of individual patient's comorbidities based on medical record alone, so neither CHA_2DS_2-VASc Score, nor HAS-BLED Score was calculated in this study.
Living in nursing facilities was documented.
To achieve a list of medications, past medical history, all available medical records were reviewed. Medications described in studies [76] as risk factors for GIB were registered: NSAIDs, steroids, COX-2 inhibitors, aldosterone antagonists, selective serotonin reuptake inhibitors (SSRIs) and proton-pump inhibitors (PPI).

Laboratory values were provided by the local facility, units and reference ranges are listed below:

Laboratory test	Measure units (SI)	Reference ranges
Thrombocytes	Gpt/l	130-400
International normalized ratio (INR)		0,9-1,3
Estimated glomerular filtration rate (GFR after CKD-EPI)	ml/min/1.73m^2	>90

Table 6: Laboratory values and their reference ranges.

It was assumed, that comparing kidney function at delivery to the hospital and at discharge, an acute kidney failure due to hypovolemia could be distinguished from a chronic loss of function, being highly relevant for the NOACs.
INR values were registered for all patients, serving as measure of therapeutic effect for VKA.

Current hospital-based study design didn't allow to determine, whether individual patient had labile INR values.

8.5.Statistical methods

The data were analyzed and graphs were built with STATISTICA 7.0 program (Stat Soft Inc., USA). As part of descriptive statistics, numerical results were presented as means ± standard deviation irrespective of distribution normality, categorical results – as percentages. Normality was tested with Shapiro-Wilk's W test (S-W test).
In hypothesis testing, normally distributed data were analyzed with two-sided Student´s t-test. For analysis of nonparametric data in independent groups Kolmogorov-Smirnov test (K-S test) was used for continuous variables. To compare nominal variables in two independent groups Chi-square ($\chi 2$) test was used with Yates's correction when appropriate. For multiple independent groups comparisons Pearson $\chi 2$ and Multiple-Likelihood (M-L) $\chi 2$ were used for nominal variables and median test $\chi 2$ for continuous variables. Dependent groups were analyzed with nonparametric Wilcoxon matched pair test.
Statistical significance was defined by $p<0.05$.

9. Results

9.1.General study collective data

9.1.1. Demographic data

Approximately 12.000 endoscopic interventions were performed in the Elblandklinikum Meissen from 01.01.2012 to 31.12.2014. 830 cases of GIB in 742 individual patients met the inclusion criteria. The number of GIB exceeds the number of patients, due to recurrent bleeding events. The mean age of all study participants was 72.6±15.1 years. The youngest participant was 20 years old and the oldest 98. There were 296 bleeding cases in 2012, compared to 258 in 2013 and 276 in 2014. Demographic data are presented in Table 7 and Figure 1. There were no statistical differences in gender between the two study groups (p>0.1, K-S test).

	GIB in patients with OACs, n=201, 24.2%	GIB in patients without OACs, n=629, 75.8%
Sex	112 male /89 female (56/44%)	362 male /267 female (58/42%)
Age (mean±SD)	77.8±9.0 years	70.9±16.2 years

Table 7: Demographic data of the study population divided in OAC and non-OAC group.

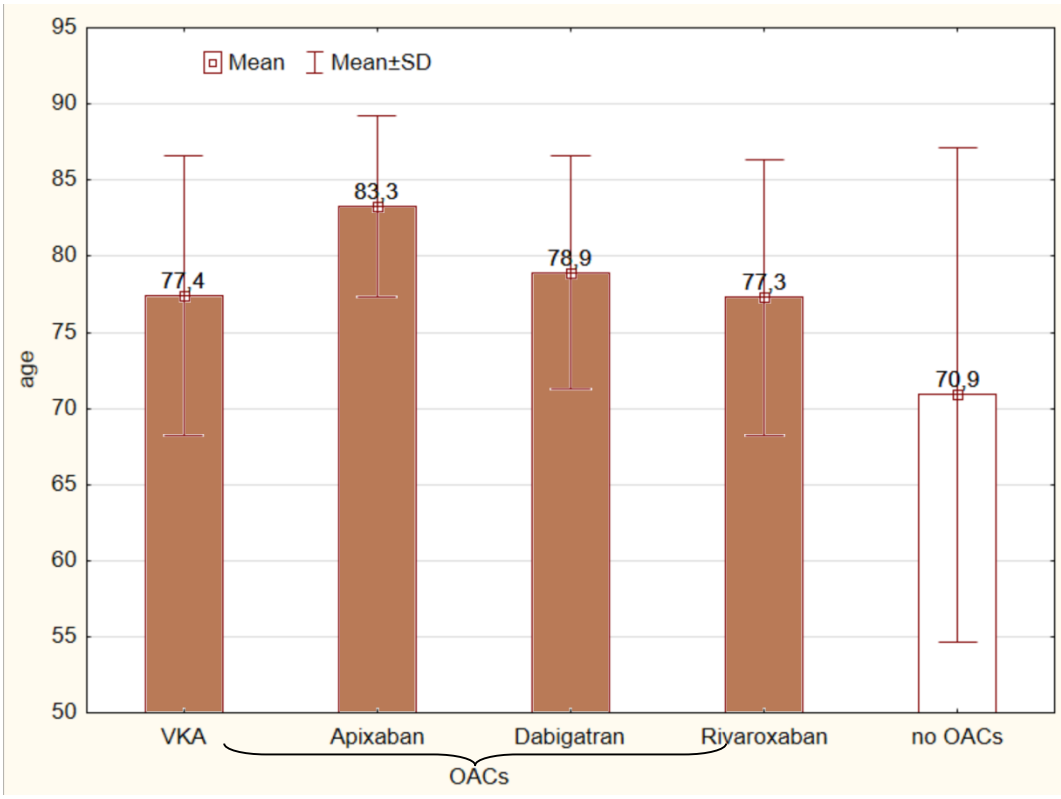


Figure 1: Mean age of patients treated with OACs, VKA and those without anticoagulants.

The group of patients receiving anticoagulation was older with the mean age of 77.8 years as compared to 70.9 years in the non-OAC group ($p<0.001$, K-S test).
14.2% of patients were referred from nursing homes, whereas 85.8% were admitted from their own houses. The proportion of patients receiving OACs was lower among nursing home residents as compared to patients living in their own houses (25.3% vs. 13.7%, $p=0.013$, $\chi 2$ test).

9.1.2. Comorbidities and co-medications

The following major comorbidities of patient collective are shown in Table 8. The majority of them suffered from diabetes, followed by ischemic heart disease, malignancies and liver cirrhosis.

Concomitant diseases	Percent of patients with comorbidity
Diabetes mellitus type I or II	36.0
Ischemic heart disease	29.9
Malignant disease	14.9
Liver cirrhosis	13.5

Table 8: Comorbidities in the study collective (all groups).

The proportion of patients with ischemic heart disease and diabetes mellitus (type I and II) was higher in the group receiving OACs than in the OAC naïve group ($p<0.001$, $\chi 2$ test).
In 22.7% cases there was at least one episode of GIB in the patient's medical history prior to the current event. However, there were no differences between all study groups: OACs vs. no OACs ($p=0.49$, $\chi 2$ test).
The medication of the study population is presented in Table 9. The use of antiplatelet drugs and heparins will be discussed in Chapter 9.7.

	No OAC	VKA	NOAC	Total
NSAIDs (except aspirin)	8.4%	3.5%	5.8%	7.5%
Steroids	2.1%	0.9%	1.2%	1.8%
COX-2 inhibitors	0.6%	0.9%	1.2%	0.7%
Aldosterone antagonists	8.9%*	20.0%	19.8%	11.6%
SSRI	2.5%	0%	2.3%	2.2%
PPI	27.0%*	35.7%	42.0%	29.8%

Table 9: Co-medications of the study population shown as percent of cases per group.
* highlighted by grey background indicates $p<0.05$ using Pearson $\chi 2$ test.

There was a generally high prevalence of PPI use before bleeding events, and the rate of PPI prescriptions in the VKA and NOAC group was higher than in the anticoagulants naïve group (p=0.003, $\chi 2$ test)

The more frequent use of aldosterone antagonists in the group of patients receiving OACs could be explained by a higher rate of heart failure in this group. However, the analysis of this comorbidity was not the task of the present study and therefore it is not further discussed.

9.2.Bleeding events

9.2.1. Clinical appearance and symptoms

Patients with acute and overt GIB symptoms at admission were immediately referred to endoscopy unit or if the bleeding became apparent during the hospital stay. In addition, some patients underwent an elective endoscopy. For study purposes, in cases with multiple symptoms, only the leading and most aggravating symptom was documented.

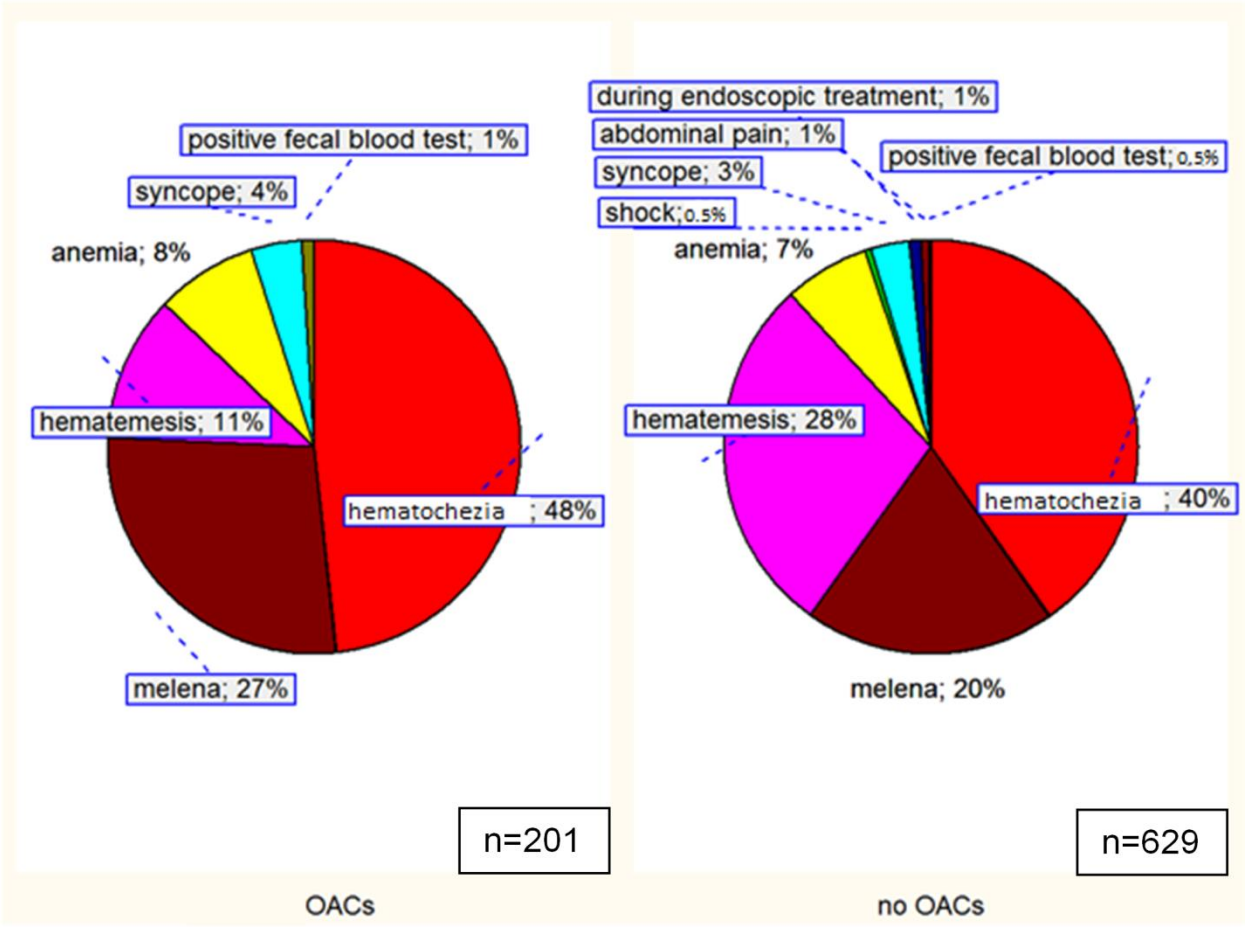


Figure 2: Leading symptoms in patients treated with oral anticoagulation.

Hematochezia and melena were present in 42% or 21% of cases, respectively; hematemesis in 24% of cases. In 27 cases (3%) syncope was the leading symptom, 3 more patients (0.4%) had

shock on admission. Anemia was the only surrogate parameter in 7%, unspecific abdominal pain in 0.7% of cases, positive fecal blood tests without any other biochemical or hematological abnormalities or symptoms in 3 cases (0.4%). The distribution of leading symptoms differed significantly between the study groups ($p<0.0001$, Pearson $\chi 2$ test), with more cases of melena, positive fecal blood tests and anemia in the OACs group and more frequent hematemesis in the non-OAC group.

9.2.2. Bleeding lesions and their nosological classification

The proportion of upper, lower and small bowel GIB is presented in the pie chart (Figure 3), while further anatomical and nosological classification are shown in Figure 4. One patient treated with VKA had two different bleeding sources: hemorrhagic colitis and hemorrhagic gastritis. This case was not considered in the final analysis.

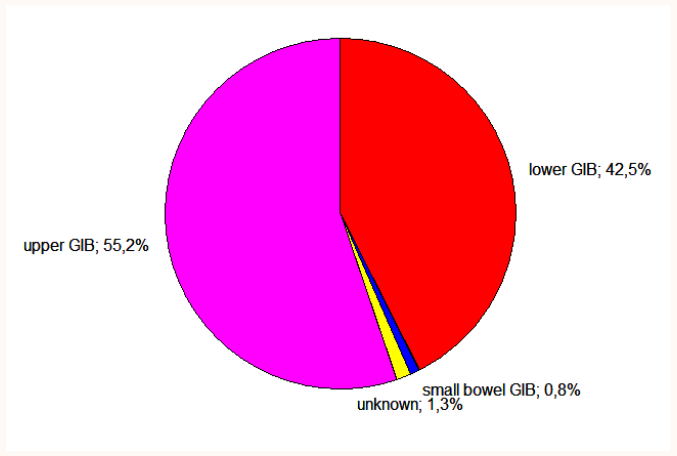


Figure 3: General localization of bleeding lesions in the GIT (upper, middle and lower GIB). Duodenal bleedings were classified as “upper GIB”, whereas “small bowel bleedings” were called only those distal to Treitz ligament.

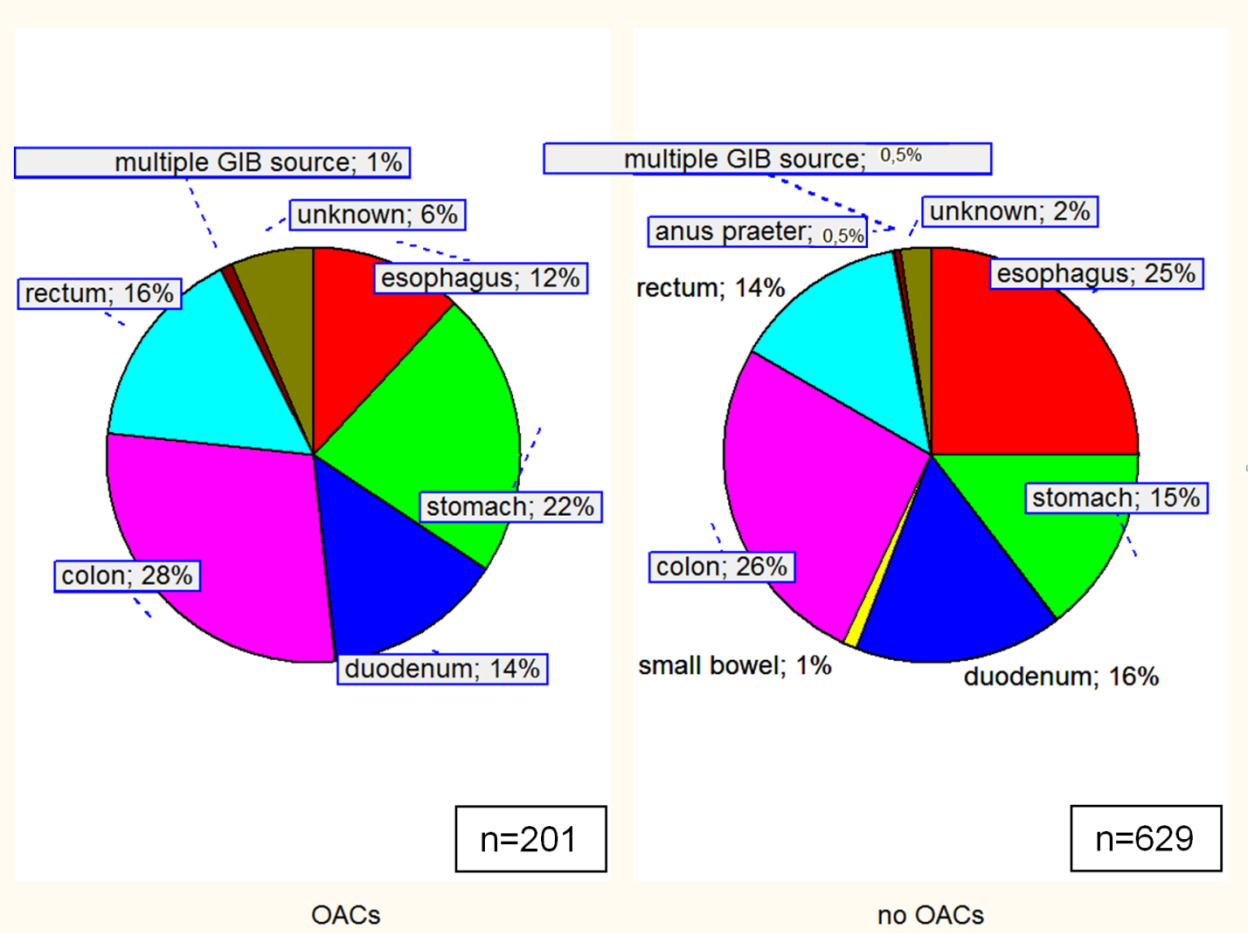


Figure 4: Detailed analysis of GI bleeding lesions by anatomical localization.

The localization of GI bleeding lesions showed differences in distribution between the study groups (p=0.0015, Pearson $\chi 2$ test), with more cases of GIB originating in the stomach and bleedings of unknown origin in the OAC group, while more frequent esophageal variceal bleedings in the OAC naïve group were identified.

There was only one case (0.5%) of variceal GIB in a patient treated with OAC (rivaroxaban for atrial fibrillation), compared to 43 (6.8%) variceal GIB in the OAC naïve group. There were fewer iatrogenic bleedings in the OAC group (p=0.03, $\chi 2$ test) for reasons discussed in Chapter 9.2.4.

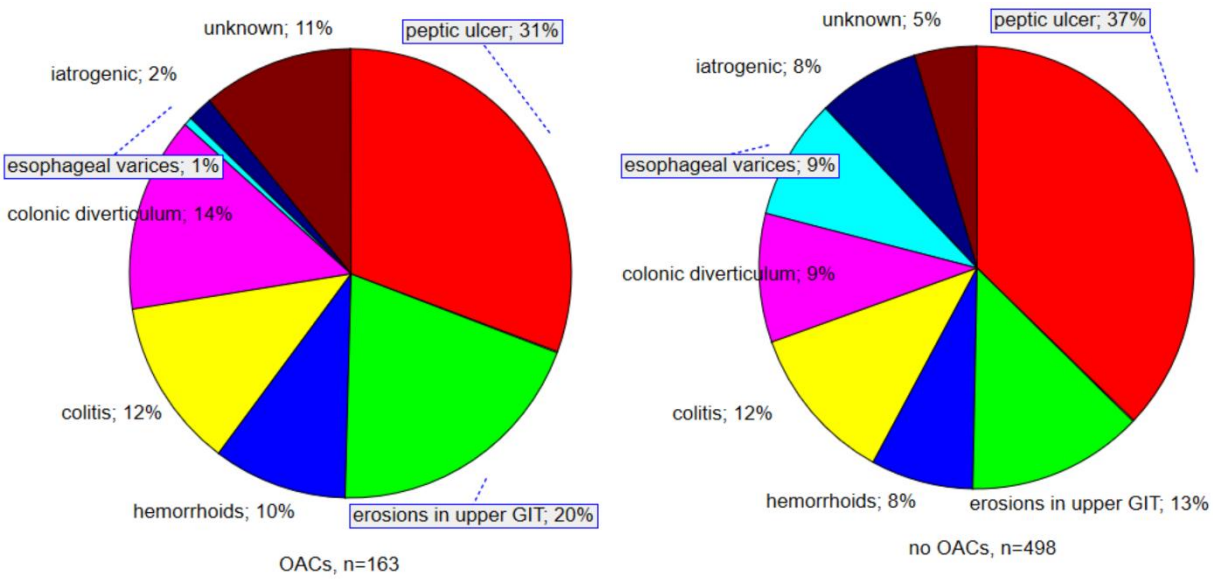


Figure 5: Sources of GIB. Only bleeding sources > 4% of total GIB bleedings are shown.

Diagnosis	Percent
Peptic ulcer	28.3
Erosions in upper GIT	11.7
Colitis	9.4
Colonic diverticulum	8.4
Hemorrhoids	6.5
Esophageal varices	5.4
Unknown source	4.9
Iatrogenic	4.9
Inflammatory bowel disease	3.1
Colonic cancer	2.0
Gastric cancer	2.0
Colonic polyp	1.9
AVM	1.7
Mallory-Weiss syndrome	1.7
Rectal ulcer	1.6
Rectal polyp	1.1
Ischemic colitis	0.8
Infiltrating pacreato-biliary cancer	0.7
Rectal cancer	0.7

Upper GIT GIST	0.7
Gastric polyp	0.7
Esophageal cancer	0.5
Colonic ulcer	0.2
Small bowel ulcer	0.2
Gastric lymphoma	0.2
Rectal stricture	0.1
Gastric lipoma	0.1

Table 10: Sources of GI bleeding. All sources of GIB < 4% of total GIB sources are highlighted by grey background (n=169, 20.4%). They were excluded from the final analysis, which summary is shown in the Figure 5.

Peptic lesions in the upper GIT (erosions and ulcers in esophagus, stomach and duodenum) were the most common bleeding sources in both study groups, accounting for 40.8% or 39.7% of bleeding events in the groups treated with or without OACs, respectively. The total number of small bowel lesions was small and comprised mainly ulcers and AVM (n=7, 0.8%), all of which detectable in the non- OACs group, only. In 60 cases (7.2%) more than one bleeding source was identified.

A rare type of bleeding lesion in the NOAC naïve group was an anus praeter ulcer (n=1). This case was classified as a colonic bleeding for the study purposes.

No bleeding lesion could be visualized in 4.9% of cases: 3% of cases in OAC naïve group, and in 9% in the OAC group. Unknown source of GIB was more often in the OAC group (p=0.005, $\chi 2$ test). In addition to that, the exact source of an overt bleeding (blood/clots present in GIT lumen) was undetectable by endoscopy in 5.3% of cases (n=44). In 36 out of 44 cases (82%) it was a suspected colonic diverticulum bleeding (this finding was seen with prevalence of 77% in the OACs group and 86% in the OAC naïve group (p=1.0, $\chi 2$ test).

A lesion with active bleeding (e.g. Forrest 1a/1b ulcers or spurting esophageal varices) was reported during the initial endoscopy in 10.2% of cases. There was no difference in the rate of active GIB among OAC naïve, VKA and NOAC patients (p>0.05, Pearson $\chi 2$ test).

9.2.3. H. pylori associated bleeding

In 31.1% of cases presenting with bleedings due to peptic ulcer disease and in 10% due to erosive gastritis, H. pylori status was available. There were 36 peptic ulcers (50.0%) and 3 erosive gastritis (33.3%) associated with H. pylori infection; among them 18 were gastric and 18

duodenal ulcers, respectively. In addition to patients with peptic ulcer disease, one case of gastric cancer and one gastric MALT lymphoma were associated with H. pylori infection.

9.2.4. Iatrogenic lesions as a separate bleeding source

Iatrogenic lesions were reported as a bleeding source in 4.9% cases (n=41). The most common source of iatrogenic bleeding was post-polypectomy (18 cases, 43.9%), either performed in our hospital or in an outpatient setting. The time interval from polypectomy to the bleeding event varied between 0 to 11 days, with the mean of 3.4 days. 2 bleeding events occurred during the polypectomy procedure. Endoscopic papillotomy was the cause of GIB in 9 cases (22.0%); in 2 out of 9 cases the bleeding occurred during the ERC procedure. There was 1 bleeding after endoscopic grasper-biopsy from stomach and 2 rectal bleedings after outpatient fine needle biopsy of the prostate. 2 GIB ulcers were reported as a consequence of chronic gastric wall irritation due to PEG several years after its placement. In 2 cases anastomositis-lesion with bleeding on the 7th and 12th days after the colonic surgeries were diagnosed. Ligation-induced ulcers in esophagus 4 days after variceal banding ligation were detectable in 2 cases and 2 other lesions after sclerotherapy of hemorrhoids. There were 3 cases of bleeding due to radiogenic proctitis; two of them were observed in the same patient at a 2-week interval.

The latter patient (71 years of age, male) was the only one with iatrogenic GIB in the (N)OAC group (rivaroxaban). The dosage of rivaroxaban was therefore reduced from 20 mg to 10 mg after the GIB event. Rivaroxaban was suspended after recurrent bleeding. Afterwards, this patient remained free of bleeding events.

All registered endoscopic interventions (e.g. ERC, polypectomy) were performed in patients when OAC therapy was withdrawn. There were no patients undergoing an urgent endoscopic intervention (e.g. papillotomy) while receiving OACs.

One patient with a mechanical aortic heart valve suffering from bleeding after polypectomy was bridged with intravenous heparin at the time of GIB, his conventional VKA was suspended.

No. of cases	Diagnosis	Time interval from the procedure to bleeding	Endoscopic therapy
18	Polypectomy bleeding in colon (n=11) and rectum (n=7)	During the procedure, up to 11 days	Clipping, adrenalin injection, fibrin injection, Hemospray® application, completion of endoscopic mucosal resection

9	Papillotomy bleeding	During the procedure, up to 10 days	Adrenalin injection
3	Radiogenic proctitis	Years	No local therapy, OAC suspension
2	Rectal lesion after fine needle biopsy of the prostate	4, 11 days	Saline injection
1	Mucosal lesion in stomach after grasper-biopsy	During the procedure	Clipping
2	Ulcer after sclerotherapy of hemorrhoids	3 days	No local therapy
2	Ulcer following banding of esophageal varices	4 days	Repeated banding and sclerosing
2	ulcer in esophagus (1) and stomach (1) due to mechanical irritation by PEG	Years	No local therapy
2	Anastomositis in colon	7, 12 days	No local therapy

Table 11: Detailed information on iatrogenic GIBs and their treatment.

9.2.5. Bleeding events among patients hospitalized for another medical condition

In 12% of cases (n=100) GIB developed during hospital admission for diseases non-related to GIB. There were 11 more patients who developed iatrogenic GIB following papillotomy, polypectomy, etc., however, they will not be included into the subgroup analysis because of different pathogenesis. The summary of main diagnoses of hospitalized patients who developed GIB is presented in the Figure 6.

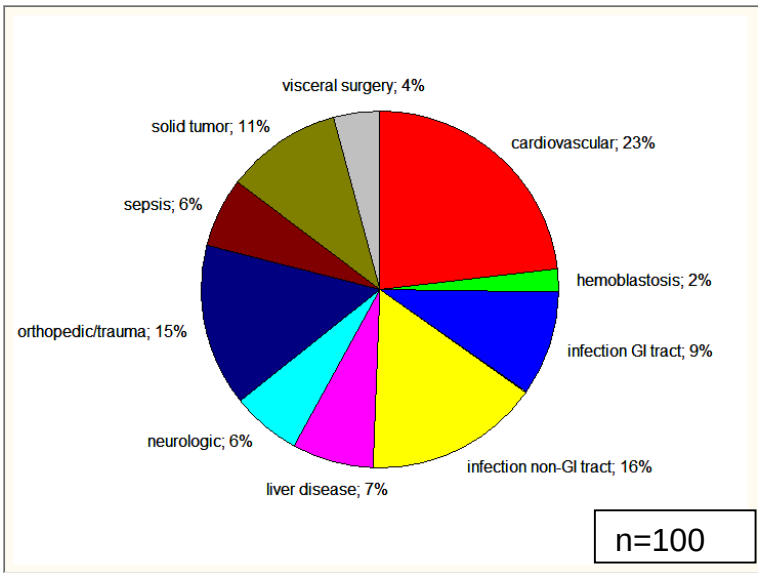


Figure 6: Main diagnoses of hospitalized patients who developed GIB during the hospital stay and were admitted due to diseases non-related to GIB.

The Figures 7 and 8 present the distribution of bleeding lesions that occurred, during hospital stay of patients admitted with bleeding non-related diagnoses and in patients admitted due to GIB.

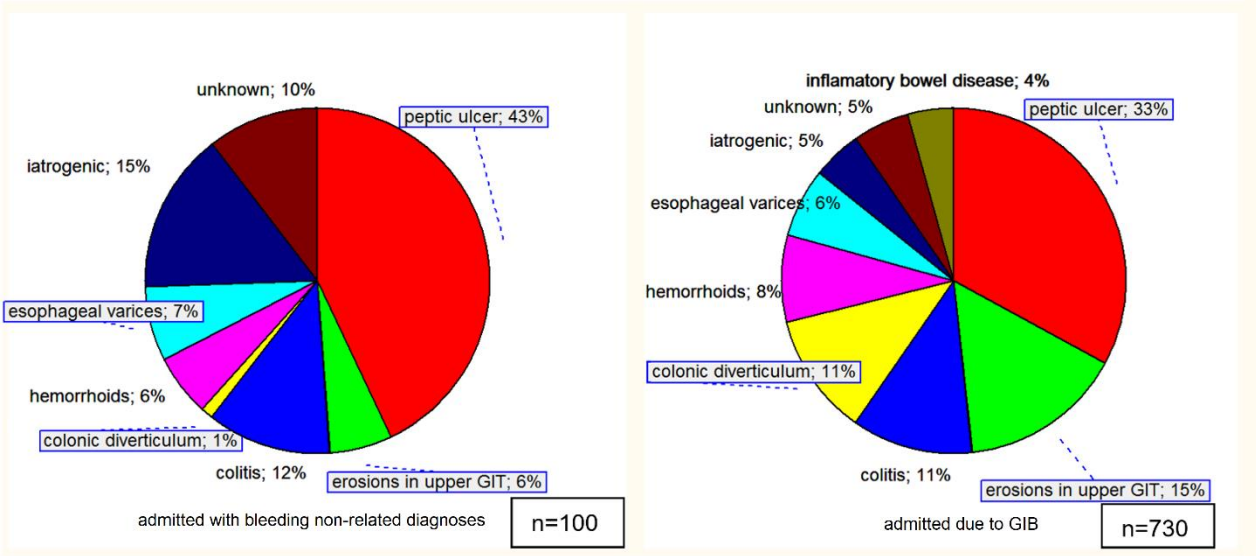


Figure 7 and Figure 8: Bleeding lesions in patients admitted due to GIB and in patients during hospital stay admitted with bleeding non-related diagnoses. For the purpose of better visualization, lesions with bleeding rate <2.5% are omitted.

Among in-hospital acquired bleeding events, the rate of peptic lesions in the upper GIT was comparable to all other study patients (49% and 48%). There were more GIB of unknown source

in in-patients: 10 vs. 5%, respectively. There were fewer diverticular bleeding events in in-hospital patients (1% vs. 11%).

Among patients who developed in-hospital GIB, 12.6% received OACs, which is less than in the whole study group (24.2%). Unfortunately, the rate of heparin users among hospitalized patients could not be reliably estimated due to insufficient medical records.

Patients with in-hospital GIB had significantly higher mortality, 21% versus 4.4% ($p<0.0001$, χ^2 test).

9.3.Oral anticoagulation

Phenprocoumon, a VKA, was the only medication of this class recorded in the study and it was the most common OAC substance in the study population. 57% of patients from the OAC group, which translates to 13.9% of all studied cases, were treated with phenprocoumon at the onset of GIB. The prevalence of the other three OACs (rivaroxaban, dabigatran and apixaban) is presented in Figure 9.

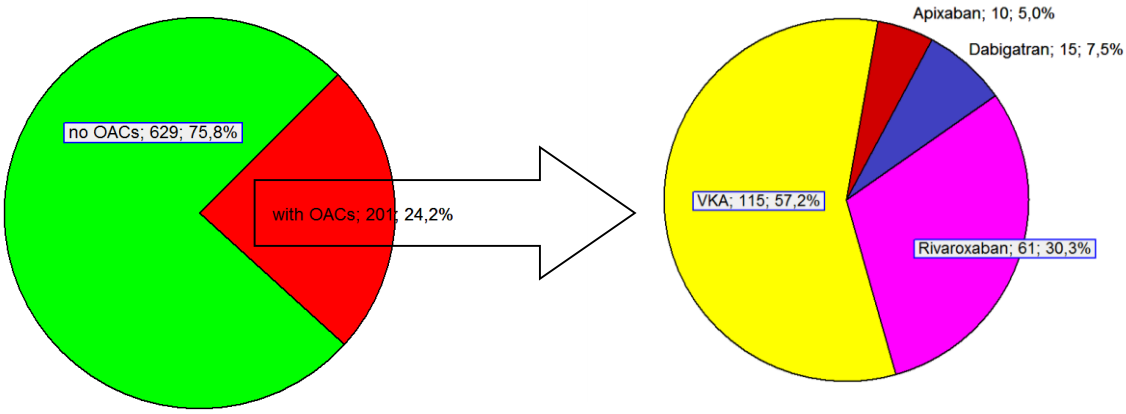


Figure 9: Prevalence of oral anticoagulants in the study population.

Indication	N (%)	Medication used, N (%)
Atrial fibrillation	164 (81.6%)	91 (57%) VKA 46 (29%) rivaroxaban 14 (9%) dabigatran 10 (6%) apixaban
Venous thromboembolism	32 (15.9%)	20 (63%) VKA 12 (37%) rivaroxaban
Mechanical heart valve	2 (1%)	VKA

Perioperative prophylaxis	2 (1%)	Rivaroxaban 10 mg once daily
Atrial thrombus	1 (0.5 %)	Dabigatran 110 mg twice daily (off-label indication)
Postoperative anticoagulation after vascular surgery	2 (1%)	1 VKA and 1 rivaroxaban
Unintentional OAC intake	1 (0.5%)	VKA

Table 12: Indications for OAC therapy.

The dosages of NOACs will be discussed later in the context of renal function impairment, Chapter 9.8. The switch between OAC medications within the observation period will be discussed in Chapter 9.12.1. “Multiple hospitalizations”.

9.4.Endoscopic studies

In all but two cases, at least one endoscopic study was performed (see the end of the paragraph for details). There were 33% urgent and 67% regularly scheduled endoscopies.

Three patients (0.4% cases) became intubated airways just before the onset of the urgent endoscopy. The mean time from admission to the first endoscopic study was 2.1±3.1 days and the range 0 to 39, with the broad distribution due to bleeding events among patients hospitalized for another medical condition. There was no difference between time to the first endoscopy between groups with/without OACs ($p>0.1$, K-S test).

In 53% cases more than one endoscopic study was performed. Reasons were to treat a recurrent bleeding, to control the results of the treatment, or to search for the primarily unidentified bleeding source. In 19% the initial endoscopy did not reveal any bleeding source. Endoscopies leading to the initial identification of bleeding sources, are provided below:

- Gastroscopy (58%)
- Colonoscopy (36%)
- Rectoscopy (3%)
- Sigmoidoscopy (2%)
- ERC (0.4%), or 4 cases, all with intraoperative GIB after endoscopic papillotomy
- Intestinoscopy (0.1%), or 1 case (other small intestinal bleedings were diagnosed and treated in external hospitals).

Two cases without any endoscopic evaluation included one terminally ill patient with a withdrawn informed consent and one patient with endoscopy, terminated due to uncontrollable motoric agitation.

9.4.1. Endoscopic therapy

Endoscopic therapy was applied in n=179 cases (21.8%); the need for endoscopic therapy did not differ neither between non-OAC and OACs nor between individual OAC groups (VKA vs. NOACs, p=0.21 and p=0.42, respectively, χ^2 tests). In 28 cases (15.6%) more than one therapeutic modality was utilized. Therapies applied during the same hospital stay, inclusive those utilized in repeated endoscopies, are described in Table 13.

Therapeutic modality	% of all therapies	number of cases
Adrenaline injection	43	78
Sclerosant (ethoxysclerol)	19	34
Endoscopic clipping	15	28
Polypectomy including EMR	15	28
Ligature banding	14	25
Fibrin injection	5	9
Hemospray®	3	6
Argon plasma coagulation	2	4
Stent	2	3
Multiple therapeutic modalities	15	28

Table 13: Summary of interventional endoscopic procedures. Note: The sum is >100% because multiple treatment modalities were performed in some cases.

Endoscopic therapy resulted in at least a temporary bleeding cessation in all but n=6 cases, accounting for 96.6% success rate. Among these 6 cases, 2 were treated with OACs. Among cases with an uncontrollable GIB during the initial endoscopy (there were n=14 more cases who did not undergo endoscopic therapy), a 60.0% mortality was observed. Among 6 patients who died from endoscopically uncontrollable bleeding, 4 patients received intentionally best supportive care only after the initial unsuccessful endoscopy.

In cases of insufficient endoscopic therapy and the presence of recurrent and/or continued bleedings, following therapies were performed: surgery, urgent transfer into a clinic equipped with an intestinoscope (hospital in Riesa, Saxony) or an angiographic facility (maximum care

hospitals in Dresden, Saxony). The Sengstaken-Blakemore tube was used as a rescue therapy in 3 out of 45 cases of variceal GIB, only. There was neither any difference of uncontrollable bleedings nor in the need for surgery between groups treated with or without OAC (p=0.49 and p=0.54, both Yate's corrected χ^2 tests).

Rescue therapy option and diagnosis	% of all patients	Number of cases	Hospital mortality / / 30-day mortality from the first endoscopy (percent)
Surgery (total count): - Stomach ulcer oversewing - Duodenal ulcer oversewing - Gastric resection (ulcer, cancer, lymphoma) - Gastrectomy (cancer) - Colonic resection (diverticular bleeding, cancer) - Hemicolectomy (amebic colitis) - Surgical proctoscopy, hemorrhoids oversewing - Hemorrhoidectomy	2.3	19 1 2 8 1 4 1 1 1	26/ 21
Blakemore tube (variceal bleeding)	0.3	3	67 / 67
Intravascular intervention (infiltrating pancreatic cancer, diverticular bleeding)	0.3	3	0 / 0
Intestinoscopy (small bowel AVM)	0.3	3	0/ 0

Table 14: Detailed statistics on rescue therapy and outcomes in recurrent and continued GIB.

Expectedly, mortality rate of patients in whom rescue therapy was needed, was with 25% higher as compared to that (6.4%) detected in the overall study population.

9.4.2. Complications of endoscopic interventions

Endoscopic procedures reviewed during this study were generally safe. Relative rate of complications could not be accurately calculated since the total number of all endoscopies in the study period was not registered. There was no mortality associated with endoscopic complications and no bleeding complications associated with the use of OACs during

endoscopy. Statistics of complications in patients receiving endoscopy for a GI bleeding or a bleeding complication of an endoscopy performed for other causes are summarized in Table 15.

Number of cases	Endoscopic procedure	Complication	Therapy/ consequences
4	Papillotomy	Bleeding	Adrenaline injection, 2 RBC units in 1 case
4	Polypectomy	Bleeding	Clipping, adrenaline injection, colon resection in 1 case
3	Gastroscopy	Motoric agitation	1 out of 3 endoscopies was terminated
1	Diagnostic colonoscopy	Sepsis	intensive care unit stay for 2 days
1	Hemorrhoids sclerosing	Ulcer building, LGIB	Local therapy, need for readmission
1	Rectum stenosis dilatation	Bleeding	Local therapy; died from other cause 2 weeks after endoscopy

Table 15: Complications of endoscopic procedures among patients included in the study.

9.5.Duration of hospital stay

Patients were hospitalized for 8.0±7.8 days on average after the initial endoscopy, with broad range between 0 to 96 days. Total hospital stay was 10.1±8.3 days. The length of hospital stay was minimally longer in the OAC group, 10.2 vs. 10.1 days. As shown in Figure 10, patients receiving dabigatran were hospitalized for a longer period after, but not before the first endoscopy ($p<0.01$, K-S test).

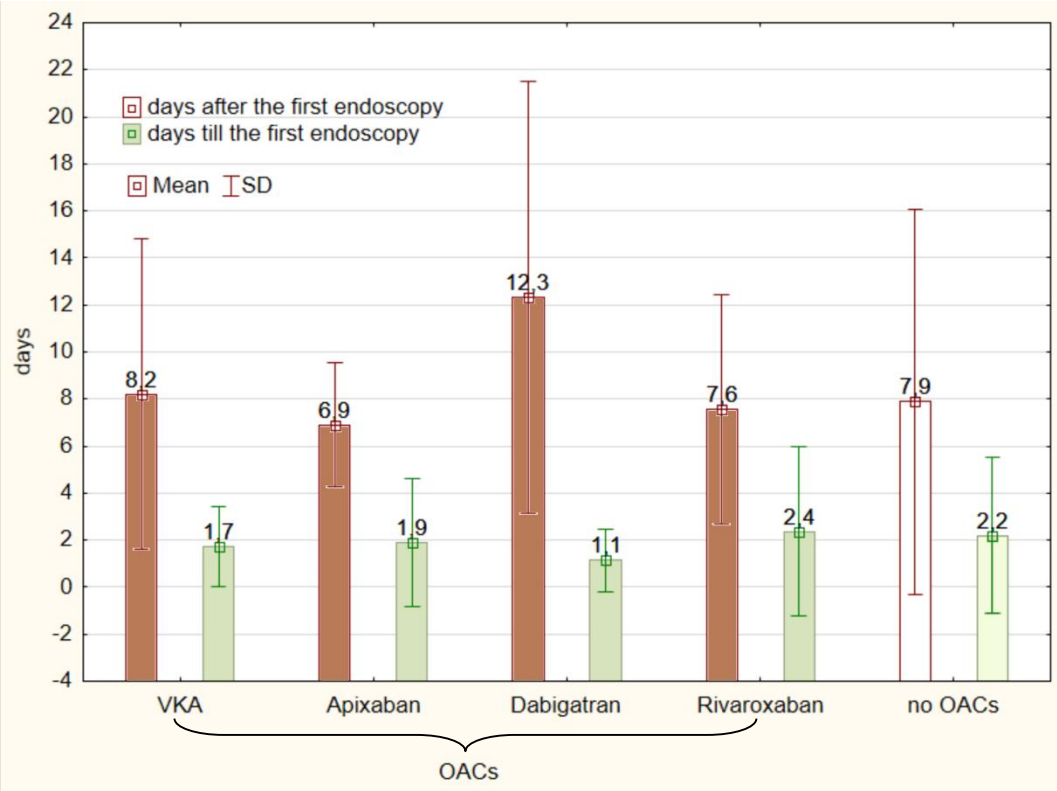


Figure 10: Length of hospitalization (days) before and after the initial endoscopy depending upon treatment with various OACs in comparison with OAC naïve patients.

9.5.1. Treatment at the intensive care unit

16.3% patients needed monitoring and therapy at the ICU; 11.4% in the OAC group and 17.8% in the OAC naïve group. Mean ICU stay was 6.2±7.2 days. There was no difference neither in the need for the treatment at the ICU, nor in the length of hospitalization at the ICU between the groups with/without OACs ($p>0.05$, χ^2 test and K-S test respectively). Figure 11 shows the length of ICU hospitalization for individuals treated with or without OACs ($p>0.05$, Pearson χ^2 test).

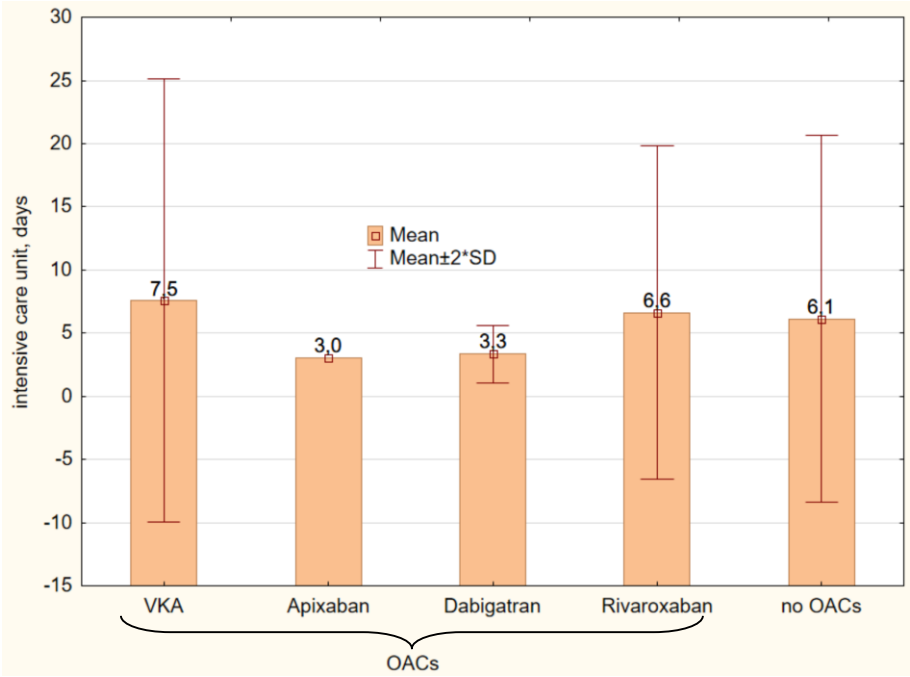


Figure 11: Length of ICU hospitalization (days) in groups treated or untreated with OAC.

Presentation with shock was observed in 16.0% (n=133) cases, and 60.9% of these patients needed an ICU stay. Shock symptoms were significantly more common in patients with UGIB than with LGIB, 21.6% vs. 8.5%, respectively ($p<0.01$, χ^2 test). Among patients with shock, the rate of OACs therapy in UGIB and LGIB (21% UGIB and 26% LGIB) was similar ($p=0.6$, χ^2 test).

9.6.Need for blood products transfusions

There were 43.3% patients (n=360) who were transfused with any type of blood components. There was no difference neither in the utilization of this therapy nor in the use of individual blood products in respect to OAC therapy applied ($p>0.1$, K-S tests). Number of patients who received at least one blood component transfused is provided in Figure 12.

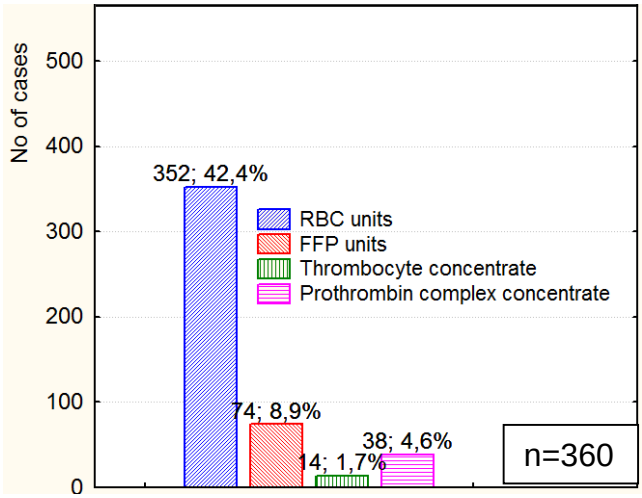


Figure 12: Summary of blood components transfused.

9.6.1. Red blood cells transfusion

Packed RBC were transfused in 42.4% cases (n=352). In the study group, 1.74 RBC units per case with the range between 2 to 72 units and interquartile range 0 to 2 RBC units were transfused. General trend in utilization of RBC units is provided below as a half-normal probability plot.

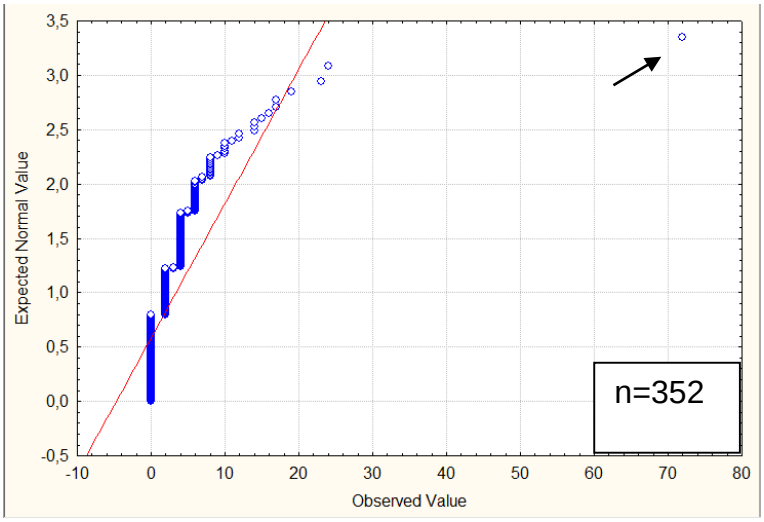


Figure 13: Half-normal probability plot of number of RBC units transfused.

The trend had one extreme value; one patient (↗) received 72 RBC and 68 FFP units. This 54-years old male ICU patient (group without OACs) with amebic colitis and sepsis developed hematochezia on the 3rd hospital day. He received diagnostic colonoscopy and a hemicolectomy was later performed. He succumbed to sepsis 40 days later.

The packed RBC utilization is shown as a 5-95 percentiles plot which encompasses only patients receiving transfusions. There was a trend towards higher RBC transfusion need in the naïve group. There was no statistically significant difference in transfused RBC units even after exclusion of the above described single outlier ($p>0.05$, K-S test).

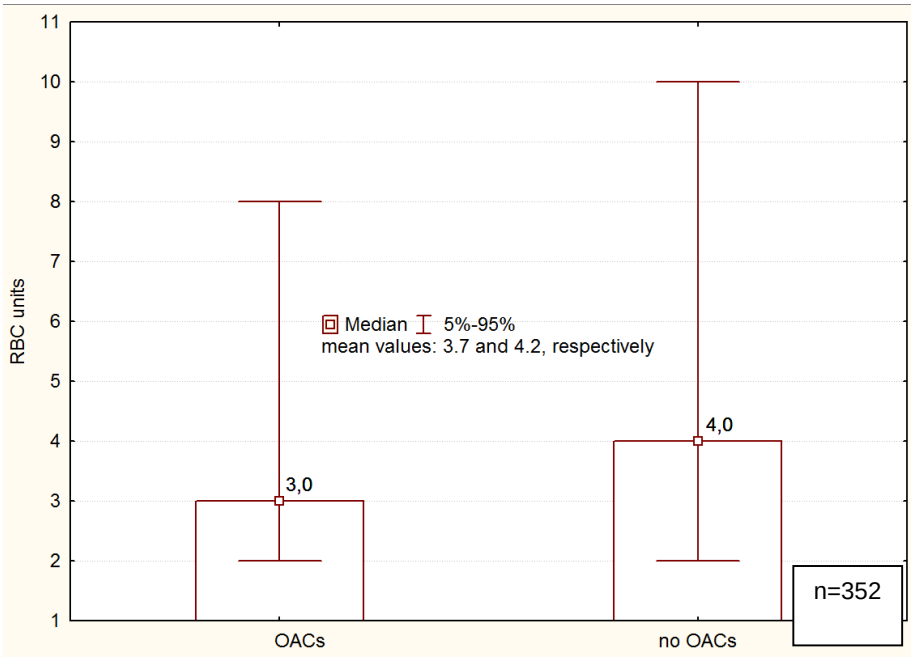


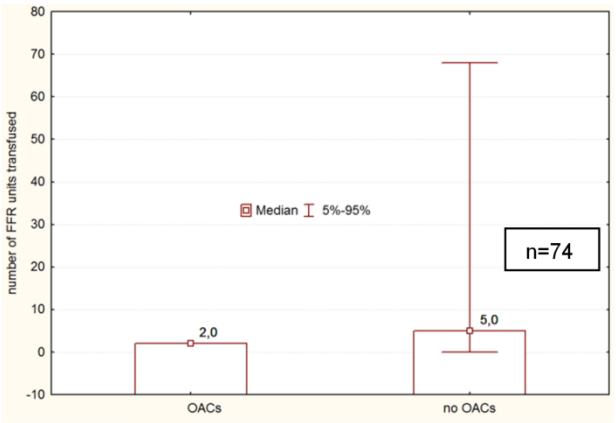
Figure 14: Number of RBC units transfused. Only patients transfused with RBC are included.

9.6.2. Administration of fresh frozen plasma, platelet concentrates and prothrombin complex concentrate

9% of all cases (n=74) needed FFPs, with the mean need of 2.5 and 3.4 FFP units in groups treated with/without OACs (the single outlier case, discussed above, was excluded from the analysis, p>0.1, K-S test).

PCs were applied in 2% cases (n=14), among them 1 case of the VKA group. There were 7 rescue therapies including 5 surgeries among patients who received PCs. The time point of transfusion relative to surgeries could not be analyzed.

Patients who received PCs were more multimorbid than an average study patient. 63% of thrombocytopenic patients had liver cirrhosis, among patients receiving PCs 28.6% had liver cirrhosis (4 of 14 cases, compared to 13.5% in the whole study group), 28.6% had malignant tumors, 57.1% patients had signs of shock at the initial presentation, 78.5% needed ICU hospitalization, and 92.9% received also RBC units, the overall mortality among patients who needed PCs transfusion was 50%.



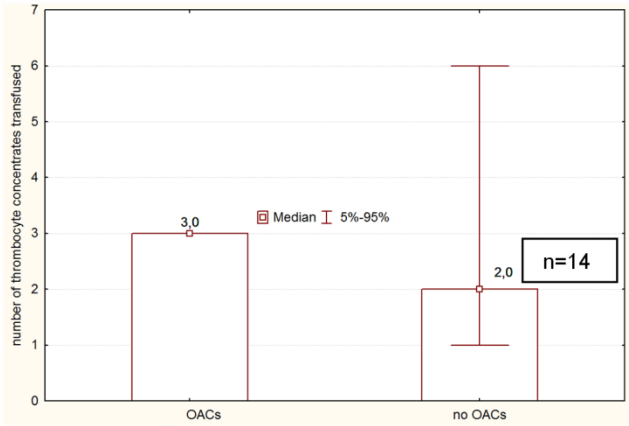


Figure 15 and Figure 16: Prevalence of transfused FFP and PCs units.

Prothrombin complex concentrate (PCC) was administered in 4.6% cases (n=38) with median dose of 2 units (500IE pro unit), range between 1 and 7 There were 25 OACs and 13 treated with OACs patients who were treated with PCCs (p=0.14, χ^2 test). In 3 patients no blood components other than PCCs were transfused. Among them was 1 patient with liver cirrhosis and variceal bleeding (INR at admission was within the normal range) and two cases had diverticular bleeding in the OAC group (INR at admission was 3.4 in both cases).

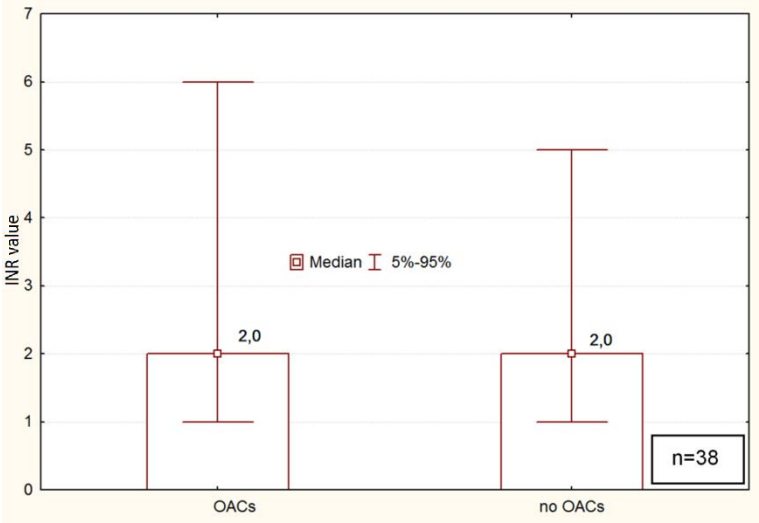


Figure 17: Utilization of PCC in OACs treated or OAC naïve patients.

9.7.Use of antiplatelet drugs and heparin

9.7.1. Antiplatelet drugs

There were 35.2% cases who received antiplatelet therapy with at least one antiplatelet drug at the time of GIB onset. A detailed analysis is shown in Table 16.

Medication	% of cases	Number of cases	Number of cases with simultaneous OACs

Aspirin monotherapy	28.9	240	16
Aspirin together with:			
Clopidogrel	2.5	21	5
Clopidogrel and cilostazol	0.2	2	
Ticagrelor	0.7	6	
Prasugrel	0.7	6	
Dipiridamol	0.6	5	1
Cilostazol	0.1	1	1
Clopidogrel monotherapy	1.2	10	
Ticlopidin monotherapy	0.1	1	

Table 16: Antiplatelet therapy in the study population.

Simultaneous therapy with antiplatelet drugs and OACs was rare in the study population. In only 1.9% cases (n=16) a combination of aspirin and an OAC was registered. In 0.8% cases (n=7) a triple anticoagulation therapy was applied: an OAC was combined with aspirin and either with clopidogrel/dipiridamol/cilostazol.

Clinical outcomes of patients treated with antiplatelet drugs, those being treated with OAC, and receiving both were compared. Data on, whether antiplatelet medications were suspended and, if so, time point to restart of their use during hospital stay could not be obtained due to insufficient medical records. However, it is known that OACs were suspended in all patients after the index bleeding event, which in most cases coincided with hospitalization.

	No OAC, no antiplatelets (n= 360)	OAC only (n= 178)	Anti-platelets only (n= 235)	Double antiplatelet therapy (n=34)	OAC and anti-platelets (n= 16)	Triple therapy (n=7)
Recurrent bleeding within index hospitalization (%)	7.5	5.6	6.8	5.9	0	0
30-day recurrent bleeding after discharge (%)	2.8	3.4	3.4	5.9	0	14.3

30-day mortality after the first endoscopy (%)	6.9	5.6	10.6	8.8	0	0
30-day readmission for any cause (%)	14.2	13.5	16.6	17.6	25.0	28.6
Duration of hospital stay in days (mean)	10.1	10.1	10.2	9.2	9.8	11.9
Duration of hospital stay after first endoscopy, days (mean)	8.0	8.2	7.8	7.4	8.3	10.7
Duration of ICU stay, days (mean)	1.3	0.8	0.8	0.9	0.1	0.6
RBC units transfused (mean)	1.9	1.6	1.6	1.9	1.5	2.9*

Table 17: Clinical outcomes depending on the use of OAC, antiplatelets, both or none. * highlighted by grey background indicates $p<0.05$, median test χ^2.

There were no statistically significant differences in the groups compared with regard to rate of a) recurrent bleeding within hospital stay and 30 days after the discharge, b) 30-day readmission after the discharge, c) 30-day mortality after the initial endoscopy ($p>0.05$ for all comparisons, Pearson χ^2 test). The use of χ^2 test in presence of a field with zero value should be noted as a possible confounding factor. There was no difference regarding the duration of the total hospital stay and hospital stay after the first endoscopy, as well as hospitalization at the ICU between groups in multiple comparisons ($p>0.05$ for all comparisons, median test χ^2). There was a difference among the groups regarding the number of RBC units transfused, with the highest number administered to patients receiving triple anticoagulation therapy ($p=0.045$, median test χ^2). This difference is shown in Figure 18.

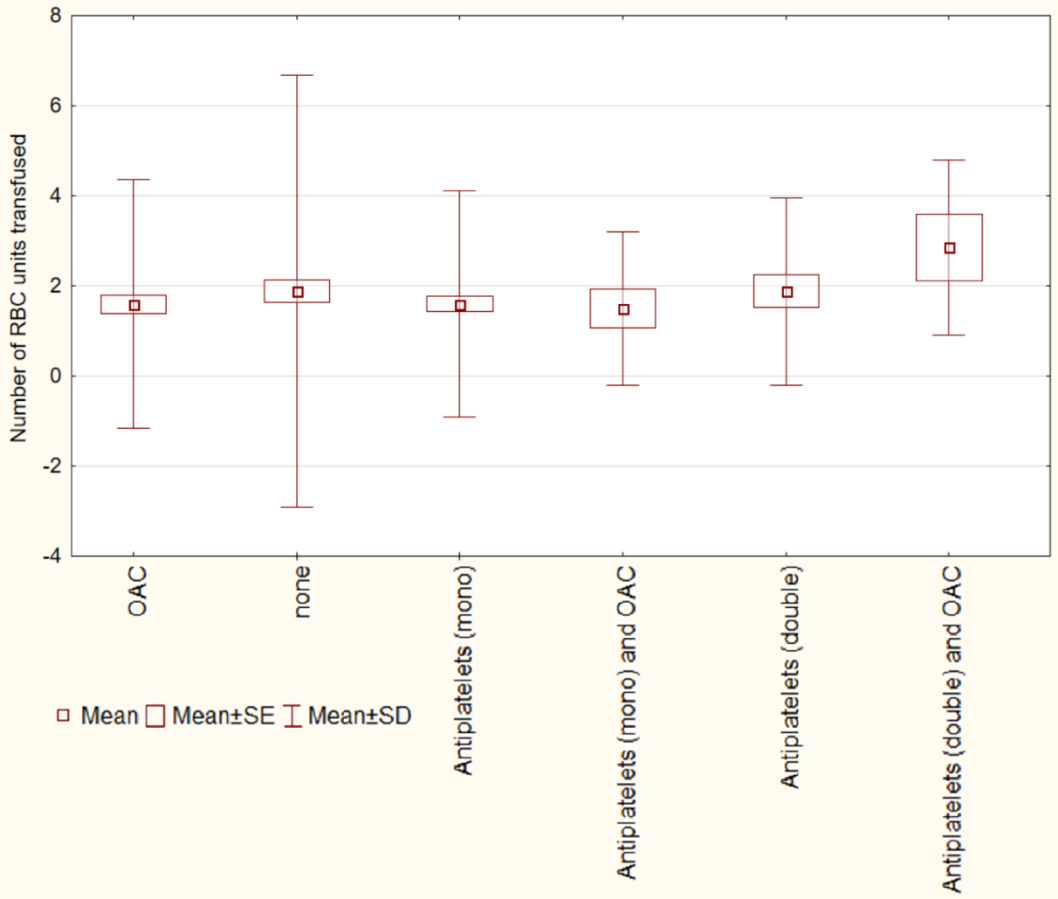


Figure 18: Number of RBC units transfused in patients treated with OAC, monotherapy and double antiplatelet therapy, triple therapy and none of these.

9.7.2. Relationship between heparin treatment and clinical outcomes of GIB

89 patients (10.7%) were treated with heparins at the time of bleeding occurrence. Due to limited medical records regarding heparin uses in both prophylactic and therapeutic dosages, LMWH and non-fractioned heparins were counted together. There were 2 patients receiving a combination of both VKA and heparins, these patients developed GIB during switching from heparins to VKA or vice versa. Patients treated with heparins were compared to the remaining participants of the study for clinically significant outcomes.

	Patients receiving heparins n=89	Patients not receiving heparins n=741
Recurrent bleeding within index hospitalization (%)	9.0	6.3

30-day recurrent bleeding after the discharge (%)	4.5	3.1
30-day mortality after the first endoscopy (%)	21.3*	5.9
30-day readmission for any cause (%)	20.2	14.6
Hospitalization days, mean	15.7*	9.4
Hospitalization after the first endoscopy, days, mean	10.6*	7.7
Hospitalization at the ICU, days, mean	2.4*	0.8
RBC units transfused, mean	2.5*	1.7

Table 18: Clinical outcomes of GIB in patients treated with heparins in both prophylactic and therapeutic dosages and heparin-naïve patients. * highlighted by grey background indicates $p<0.05$, χ^2 test and K-S test.

There was no difference between groups treated with or without heparins regarding the rate of recurrent bleeding within hospital stay and 30 days after the discharge; the readmission rate was also similar ($p>0.05$ in all comparisons, χ^2 test). The mortality rate within 30 days after the initial endoscopy was higher in patients treated with heparins ($p<0.01$, χ^2 test). Statistically significant differences were also detected in the total length of stay, length of stay after the first endoscopy, ICU stay and administration of RBC units ($p<0.01$ for all comparisons, χ^2 test). 63% of patients with GIB during the hospitalization were treated with heparins. An in-hospital development of GIB is as an established negative prognostic factor for GIB outcomes.

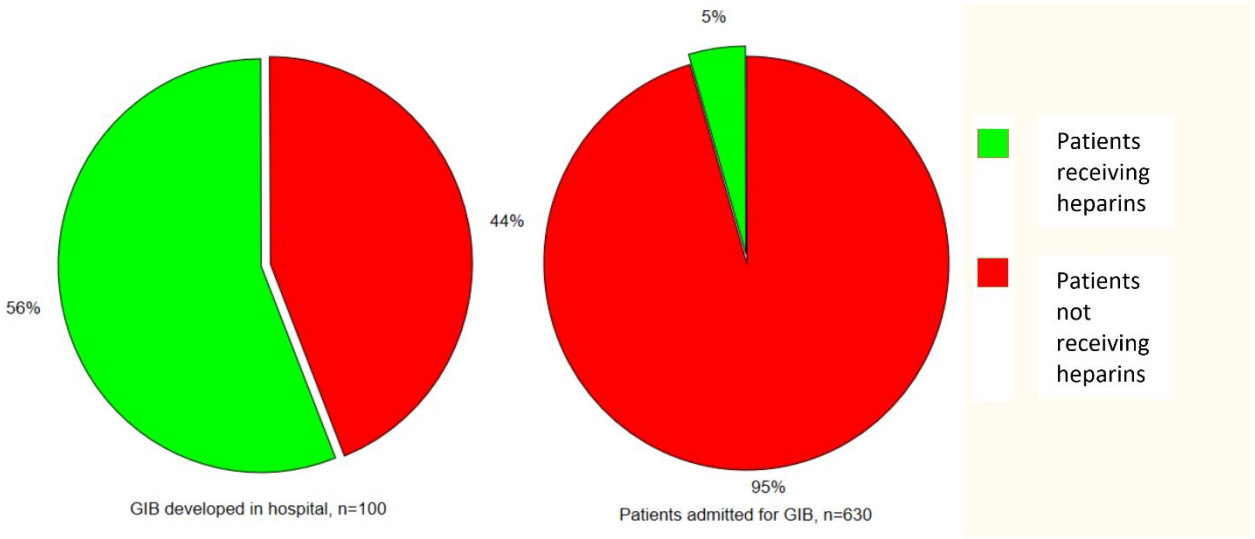
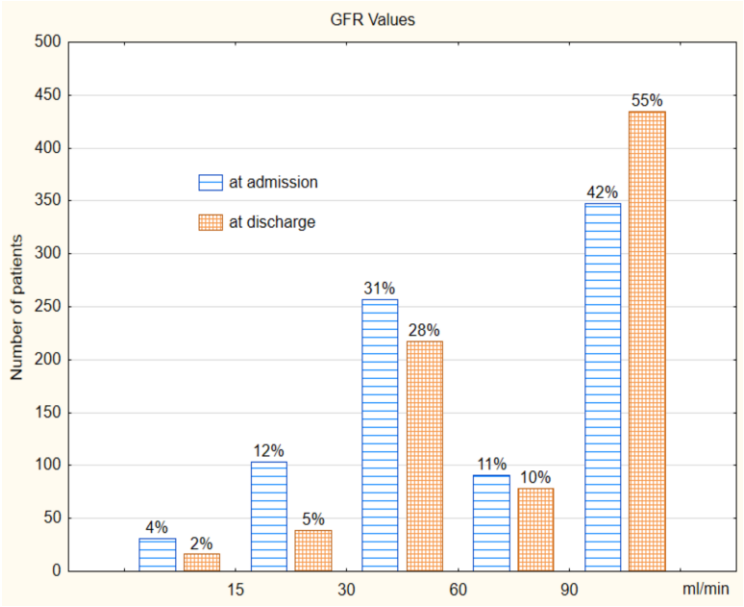


Figure 19: Proportion of patients receiving heparins who developed GIB admitted with bleeding non-related diagnoses and those admitted for GIB.

9.8.Renal function and NOAC dosages

In all patients the renal function was assessed by estimating a GFR at admission and the time point closest to discharge. In patients who developed GIB within hospitalization for other diseases, the time nearest to the bleeding onset was considered. For patients who died in hospital only initial GFR values were considered.

The assumption was, that patients suffering from bleeding had volume depletion, leading to renal failure, which was susceptible to correction during the hospitalization. Further analysis was performed according to the existing dosage adjustment rules and contraindications for NOACs in case of renal function impairment [50]. Information regarding doses of NOACs based on the history taking at admission was compared with the renal function at admission and at discharge. The distribution of GFR at admission and at discharge is presented in Figures 20 and 21.



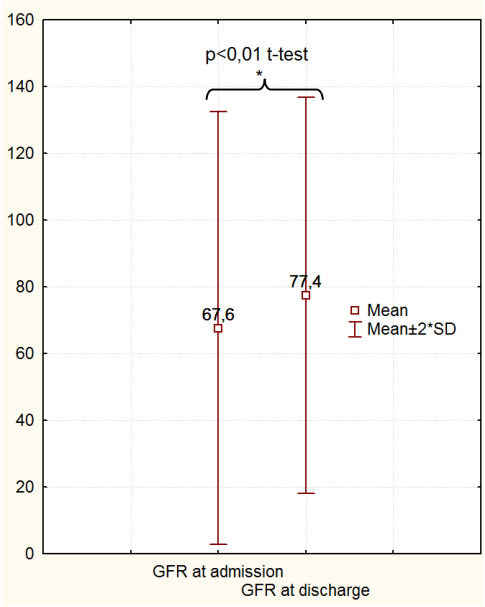


Figure 20 and Figure 21: GFR (ml/min) in the study population at admission and at discharge.

There was a statistically significant difference between GFR values at admission, mean 67.6ml/h, and at discharge, mean 77.4ml/h ($p<0.01$, Wilcoxon matched pairs test). Furthermore, among patients with shock symptoms, mean GFR values at admission (but not at discharge) were significantly lower as compared to patients without shock symptoms (64.4 vs. 68.2ml/h, $p<0.05$, K-S test). Renal function impairment was associated with poorer outcomes, patients with GFR at admission <30 ml/min had mortality 16.7% compared to 4.6% with GFR≥30ml/h ($p<0.0001$, $\chi 2$ test). There was no significant difference between NOAC, VKA users and naïve patients ($p>0.05$, $\chi 2$ test).

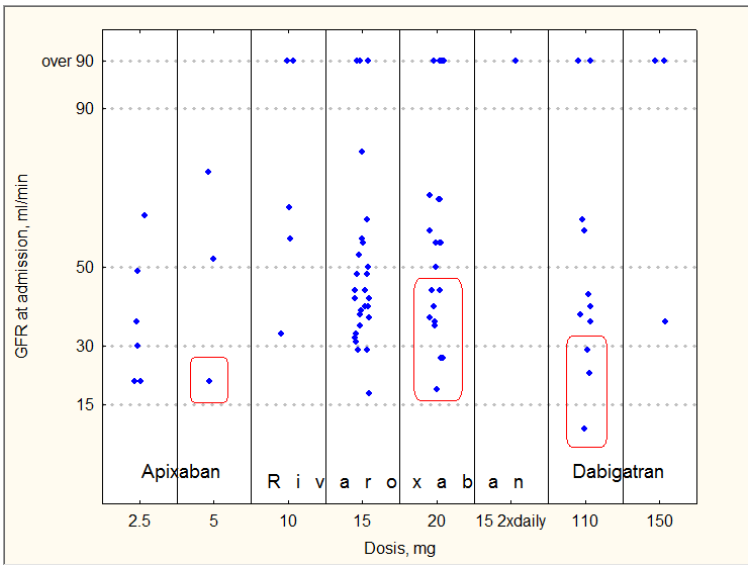


Figure 22: GFR values at admission depending upon different NOACs and their doses. Every dot shows a single individual (marked areas are described in text below).

As seen in the marked areas on the variability plot above (Figure 22), there were 14 patients (16.3%) out of 86 receiving NOACs who had lower GFR at hospital admission than approved for the respective substance and dosage used. This may suggest a high probability of drug cumulation in the body. Outcomes of these 14 cases was not significantly different from the outcomes of the other NOAC patients regarding mortality, active bleeding on endoscopy, rebleeding rates or RBC utilization (p>0.1, K-S test). The distribution of bleeding lesions in these 14 patients with possible anticoagulation effects cumulation did not follow any specific pattern: 4 were due to upper GIT erosions, 3 hemorrhoidal bleedings, 2 colitis, 1 colonic polyp, 1 Mallory-Weiss lesion, and multiple bleeding sources in 1 case (hemorrhoids and esophagitis II°). Notably, there were no peptic ulcers – the most frequent lesion in the whole study population - among these patients.

The following figures presents GFR values at discharge:

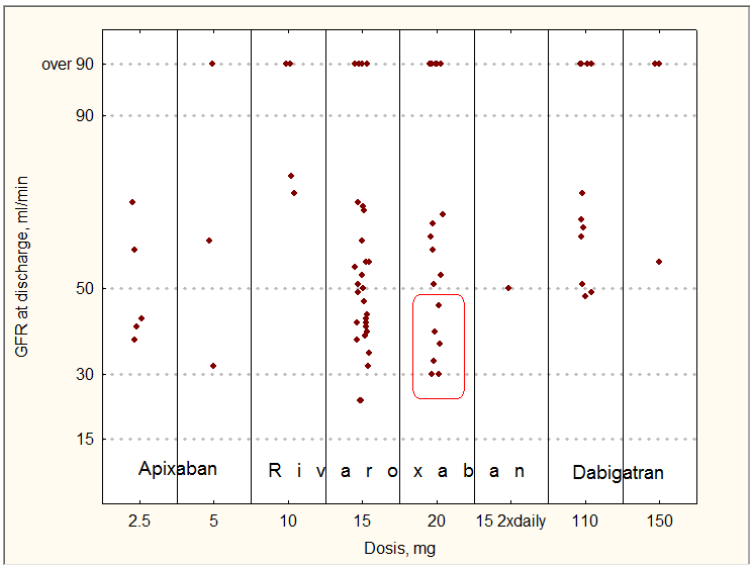


Figure 23: GFR values at discharge depending upon different NOACs and their doses. Every dot shows a single individual.

Marked dots on the variability plot (Figure 23) represent patients with GFR on the day of their discharge from the hospital in whom GFR values were incompatible with the approved doses of NOAC therapy, in particularly GFR< 49 ml/min for rivaroxaban dose of 20 mg daily. The information, whether NOAC medication was resumed at its initial dose or if the renal function had improved after the discharge from the hospital could not be obtained in the present study design.

9.9.INR values in the study population

9.9.1. INR values and anticoagulation therapy

Distribution of INR values in the study population is presented as a variability plot (Figure 24), common INR therapeutic ranges are marked on the vertical axis. Cases with apixaban and dabigatran therapy were not included for better visualization purposes, since all INR values in those cases were normal.

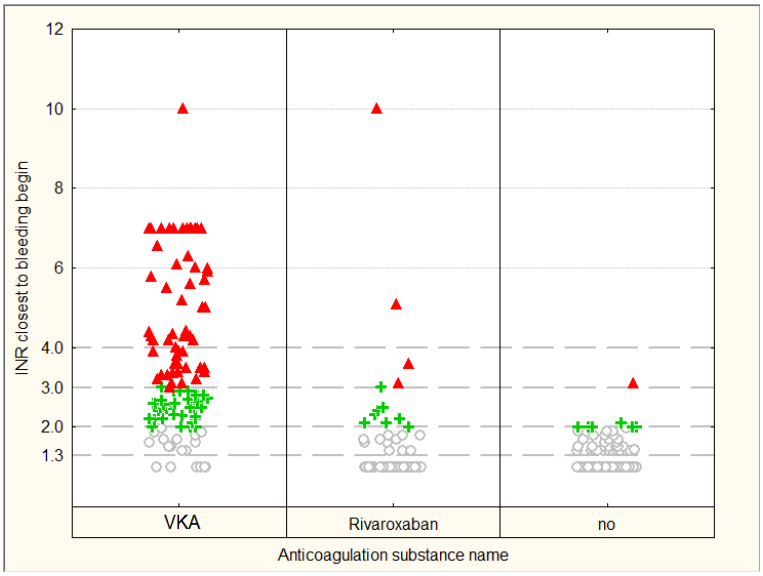


Figure 24: INR values closest to the onset of bleeding. Every marker shows a single individual. Cases marked **red** are with INR over 3.0, further addressed as "supratherapeutic range",

green: 3.0≥INR≥2.0, or "within therapeutic range",

gray: INR < 2.0 inclusive normal values, or "subtherapeutic" values.

There were 34% patients treated with VKA who had INR in therapeutic range at the onset of bleeding, 50% had INR in supratherapeutic range, the remaining16% had INR below the therapeutic range. There were 6 other patients with elevated INR who were not treated with VKA, all of them had advanced liver cirrhosis.

Among patients treated with rivaroxaban, 13.3% (n=8) had INR values between 2.0 and 3.0 and 6.7% (n=4) had INR>3.0, which is a well-known effect of this medication, yet not approved for drug effects monitoring. In 2 out of 4 rivaroxaban-patients with INR >3.0, the dosage of this medication was higher than recommended for their renal function (GFR) registered at admission.

9.9.2. Diagnoses and outcomes in OAC-patients having therapeutic and supratherapeutic INR

95 patients (83%) treated with VKA had an INR ≥2.0 at least within therapeutic range or higher, n=55 (57.8%) had supratherapeutic INR values at the onset of bleeding. Among them, 2 patients (2.1%) developed bleeding events during hospital stay admitted with bleeding non-related

diagnoses. The prevalence of bleeding lesions and clinical outcomes of patients receiving VKA were compared between patients with therapeutic vs. supratherapeutic INR values.
Patients with elevated INR due of hepatic incapacity were not included in this comparison because of different pathophysiological background. In addition, patients treated with NOACs were excluded, because INR is does not represent a valid surrogate parameter of NOAC therapy
The results of these comparisons are shown in Table 19.

	INR 2.0 to 3.0 n=38		INR >3.0 n=57	
5 most common bleeding lesions (%)	Peptic ulcer Colonic diverticulum Haemorrhoids Polyp (3 colon, 1 stomach) Erosion in upper GIT	21.1 15.8 13.2 10.5 10.5	Peptic ulcer Erosion in upper GIT Colitis Unknown Colonic diverticulum	35.1 26.3 12.3 12.3 7.0
Recurrent bleeding within index hospitalization (%)	5.3		0	
30-day recurrent bleeding after the discharge (%)	2.6		5.3	
30-day mortality after the first endoscopy (%)	0		8.8*	
30-day readmission for any cause (%)	2.6		17.5*	
Total hospital stay, days, mean	9.3		10.7 *	
ICU stay, days, mean	0.5		1.1	
RBC units transfused, mean	1.5		2.1	

Table 19: Clinical outcomes relative to INR values in patients receiving VKA. * highlighted by grey background indicates $p<0.05$.

There was no difference regarding the rate of recurrent bleeding, no difference in the number of RBC units transfused, and ICU stay between patients with therapeutic and supratherapeutic INR values ($p>0.05$, K-S test). There was a higher mortality rate 30 days after the endoscopy, readmission rate within 30 days after the discharge and a longer mean hospital stay in the group with INR>3.0 ($p<0.05$, M-L χ^2 test, K-S test, a possible limitation of the χ^2 test used: zero values in table fields should be noted).

9.10. Recurrent bleeding within index hospitalization and within 30 days after the discharge

There were rebleeding events in 55 cases (6.6%) within the same hospital stay and n=27 (3.3%) more had a recurrent bleeding 30 days after the discharge. The time from the initial endoscopy to the onset of the recurrent GIB ranged widely between 0 and 24 days, with the median of 2 days and the mean of 3.7 ±4.1 days. The OAC was suspended in all patients hospitalized for GIB. A subgroup comparison showed no significant difference either in rebleeding rates within the same hospitalization or within 30 days after the discharge between patients regardless of initial treatment with OACs ($p>0.27$ for both comparisons, χ^2 test).

The current study design provided little data, on whether/when the OAC therapy (substance, dosage) was resumed following hospital discharge after the initial bleeding. The decision was left to patient's general practitioner.

There were 19 patients (2.6%) with GIB episodes after resumption of OAC therapy after the discharge from the hospital. In 4 of these patients original OACs were exchanged against other OACs; this aspect will be discussed in Chapter 9.12.1.

9.10.1. Mortality and recurrent GIB

Both the mortality rate within hospital stay among patients with recurrent GIB was 34.5% or 19/55, which was dramatically higher, than in cases with a single episode of GIB, 4.4% ($p<0.001$, χ^2 test); in 11 out of 19 cases (58%) the bleeding was the cause of death. There were 2 patients treated with OACs (one apixaban and one VKA) among the aforementioned 19 lethal outcomes; a valid statistical comparison of patients with and without OACs was not possible because of the small sample size ($p=0.48$, Yate's corrected χ^2 test).

9.11. Readmissions for non-GIB events

There were 126 (15.2% cases) readmissions for various diseases after the initial hospitalization due to GIB within 30 days after the discharge from the hospital. 21.4% of these readmissions were due to recurrent (or new) GIB, whereas 78.6% had another reasons to be admitted. The

distribution of readmissions for non-GIB events 30 days after the initial discharge did not reveal any association with the presence of OAC therapy at the onset of initial bleeding (p=0.8, χ^2 test).

9.12. Multiple hospitalizations

There were 73 individual patients (9.8%) with recurrent GIB, with a median of 2 events per person and a maximum of 5 GIB events within the study period. Assessment with a Pearson χ^2 test could not reveal any impact of OAC before the first bleeding event as a significant risk factor for a recurrent GIB (p>0.05). Comparisons of individual NOACs and VKA, as well as group comparison “any OAC” vs. “no OAC” yielded statistical non-significant results.

9.12.1. Changes in OAC therapy in patients with multiple hospitalizations

A decision to change OAC therapy was always the responsibility of the general practitioner or cardiologist. The rationale for exchange was not described in the hospital medical record. A switch from one substance to another or a new prescription of an OAC within the study period was detected in 6 patients (0.8%), only.

There were 2 cases with a switch from VKA to rivaroxaban (both for atrial fibrillation): one case had a GIB due to a gastric polyp and the latter one a recurrent post polypectomy GIB the other patient had two episodes of LGIB in 3-months interval associated with diverticulosis and colitis.

In two cases VKA and dabigatran were suspended. In the first case, a patient (58 years of age, male) with advanced liver cirrhosis, treated with VKA due to pulmonary embolism, had an erosive hemorrhagic esophagitis. 2 months later a recurrent bleeding from the same source occurred. The patient received aspirin 100 mg daily at that time and VKA therapy was suspended, though his INR by admission was 3.1, indicating an insufficient synthesis capacity of the liver. The second patient (74 years of age, male) received dabigatran because of atrial fibrillation and was initially admitted to hospital with GIB from ulcers in stomach and duodenum. NOAC was suspended after the discharge. 2 weeks later this patient was treated with chemotherapy for hepatocellular carcinoma and developed an in-hospital GIB due to duodenal ulcer. Notably, INR was normal in both episodes and the result of H. pylori test was also negative.

Another patient (51 years of age, female) initially OACs naïve, had a hemorrhagic gastritis associated UGIB; 6 months later she received VKA therapy for the newly implanted mechanical heart valve and developed subsequently colitis associated LGIB. INR of this patient was 7.0 at admission.

One more patient (76 years of age, female) with 4 hospitalizations had initial UGIB due to gastric ulcer while being treated with VKA because of atrial fibrillation. She developed LGIB

approx.10 months later, while being treated with rivaroxaban: first a suspected diverticular GIB was described, and 3 weeks later LGIB from colonic AVM was detected. The 4th GIB episode from a gastric AVM, another 3 months later occurred after complete suspension of OAC therapy. Thus, GIBs from the AVM in upper and lower GIT were registered with VKA, NOACs and without OACs in this patient.

9.13. Overall and 30-day mortality, diagnoses

There was 6.4% mortality within hospital stay and 7.6% within 30 days after the initial endoscopy. 7.8% of patients died either within the index hospitalization or 30 days after the initial endoscopy. There was a higher mortality rate (within hospital stay) not treated with any OAC as compared to those treated with OACs (p=0.04, M-L χ^2 test), Figure 25.

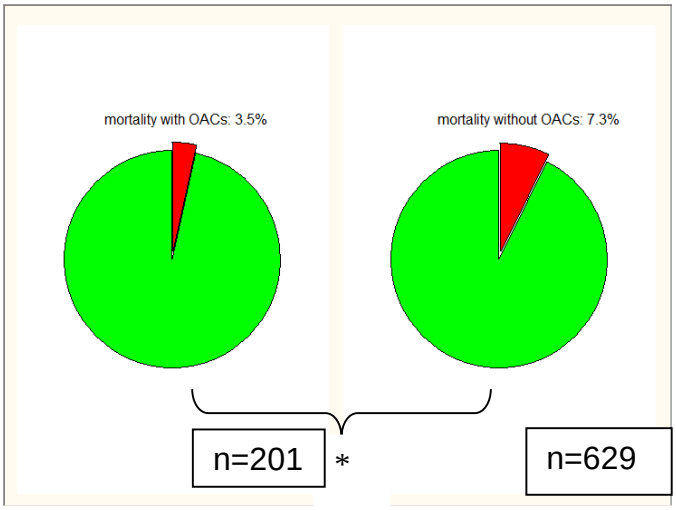
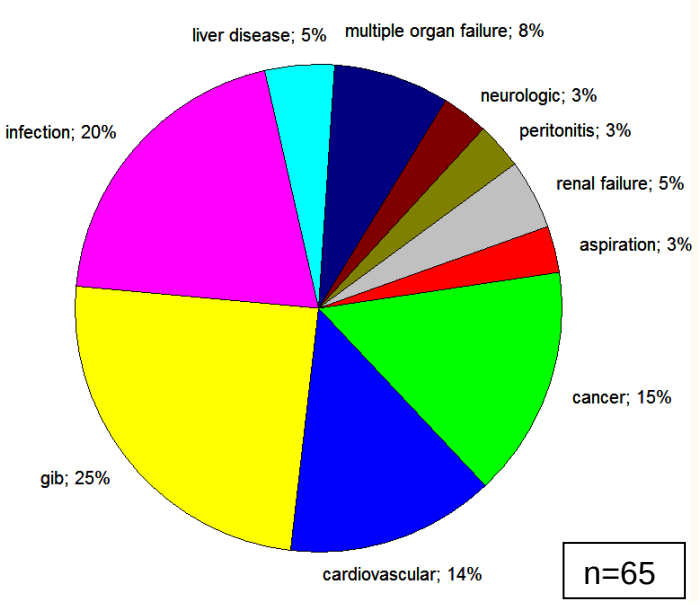


Figure 25: Mortality rates of hospitalized patients treated with or without OACs.
*[asterisk] indicates p<0.05, M-L χ^2 test.

Death causes were further analyzed and are shown in Figure 26 and Table 20.

Group of mortality cause	Percent 65
GIB	24.6
Infection incl. sepsis	20
Malignant tumor	15.4
Cardiovascular diseases	13.8
Multiple organ failure	7.7
Liver disease	4.6
Renal failure	4.6



Peritonitis	3.1
Neurologic	3.1
Aspiration	3.1

Table 20 and Figure 26: Causes of mortality according to nosological groups.

There was no statistically significant difference in the prevalence of mortality causes relative to the presence of OACs ($p>0.24$, M-L test). The comparison of subgroups: patients receiving VKA, NOACs (each of the substances or as a class name) or none of these - did not reveal statistically significant difference in case mortality rate or in mortality rate at 30-day point ($p>0.1$, M-L test).

30-day mortality causes in group treated with VKA, n=6		30-day mortality causes in group treated with NOACs, n=4	
Diagnosis	n (%)	Diagnosis	n (%)
GIB	1 (17)	GIB	2 (50)
Malignant tumor	1 (17)	Multiple organ failure	1 (25)
Cardiovascular diseases	1 (17)	Aspiration	1 (25)
Multiple organ failure	1 (17)		
Renal failure	1 (17)		
Neurologic	1 (17)		

Table 21: Mortality causes in study subgroups.

Mortality causes (either within hospital stay or 30 days after the first endoscopy) in VKA and NOAC groups are presented in Table 21. No specific pattern could be detected, possibly because of a relatively small number of fatal outcomes.

10. Discussion

As of today, analyzes of GIB with focus on VKA/NOAC therapy based on the observation of current practice in a single hospital in a rural region of Saxony are lacking. A study analyzing the outcomes of endoscopic GIB treatment in a single primary care regional hospital in Delitzsch (26,000 citizens) Saxony, in 1995-1999, when no NOACs were yet on the market, did not investigate an influence of VKA use. There were 555 urgent upper endoscopies in 5 years of observation, with 9.4% recurrent UGIB in non-variceal arm and 48.8% recurrent GIB among variceal UGIB; there were 1.1% surgeries and overall mortality rate was 3.4%. The study

focused on peptic ulcer bleeding treatment with PPI and interventional endoscopy, rapidly developing in that time period [85]. In 2005, a multicenter (21 secondary and tertiary hospitals) prospective cohort study was performed in the administrative district of Dresden, Saxony, which encompassed a part of the study population of the present study. All VKA-associated bleeding events recorded in 2005, among them 24.5% GIBs, 14.1% ICB, 23.1% hematomas, 10.3% epistaxis, 9.7% hematuria and other, were analyzed [68].

From August 2014, a series of publications by Dr. Beyer-Westendorf and his study team appeared, based on the ongoing Dresdner NOAC registry, which was initiated in October 2011 [3, 4, 66, 86]. The study is multicenter and includes data collected from over 230 physician offices, rural clinics, at least two high-capacity facilities, and a university hospital in the same geographical region.

The present study with representative 830 cases of GIB was focused on prevalence and therapy outcomes of GIB treated in a rural hospital in Saxony over the period of 01.2012 – 12.2014, with an emphasis on VKA and NOACs.

The main outcome of the study is the established high prevalence of OAC use in patients admitted to the hospital due to GIB, reaching all together 24.2%. Among them, 13.8% of the patients were treated with VKA and 10.4% with NOACs.

We observed 55.2% of UGIB, 42.5% of LGIB, and 0.8% bleedings from small intestine. In 1.3% bleedings the source could not be established.

Among patients with UGIB (n=458), 21.8% were taking OACs: 13.3% were treated with VKA and 8.5% - NOACs. The proportion of different NOAC substances was as follows: dabigatran - 15%, apixaban - 16%, and rivaroxaban - 67%.

Among patients (n=353) with LGIB, 27.1% of were treated with OACs: 14.1% with VKA and 13.0% with NOACs. 6% of the NOAC group was treated with apixaban, 20% with dabigatran and 74% with rivaroxaban.

In present study most of clinical outcomes of patients taking VKA did not significantly differ from those taking NOACs: recurrent bleeding rate, endoscopic treatment success, need for surgery, transfusion of blood components, ICU stay, readmission 30 days from discharge did not differ between NOAC and VKA groups.

Hospital mortality rate was the only clinically significant parameter differing between naïve patients and those taking any OAC: 7.9% and 3.6% respectively, the statistical significance of the difference was no more present when mortality on day 30 after the first endoscopy was analyzed.

10.1. Study design

Most studies that provided data on GIB outcomes were population-based, where patients receiving OACs formed only one of the subgroups, for example, the British GIB audit [17], Canadian RUGBE trial [29], Spanish [45], and Dutch [10] trials. Their results demonstrated possible effects of VKA/NOAC on GIB outcomes but were not appropriate for calculating relative GIB risks of anticoagulation therapy.

The other type of studies focused on VKA and NOACs focusing to determine their side effects, e. g. GIB, such as Danish register study [1, 8], two US ATRIA cohorts [82], insurance registry studies in the US with over 250,000 enrollees [63, 78], as well as Dresden NOAC registry [3, 4], and the largest pivotal Phase III NOAC studies [55-58]. The population in both types of studies was mixed, rural and urban, whereby the data from small rural hospitals only were missing.

A registry study covering a robust population of 20 million patients with 115,000 UGIB cases provided data on risk factors for UGIB and possible drug interactions between NSAIDs, low-dose aspirin, COX2-inhibotors, OACs and antiplatelets, although data on individual clinical outcomes were not available [76].

Unlike other studies that recorded clinical outcomes in a single observation year, the present study focused on validated individual outcomes of patients over 3.5 years. A long observation time and minimal lost to follow-up is more specific for population studies which yield reliable data on repeated GIB, which is often overlooked in shorter studies [9]. A long observation period of individual patients provided important information on the natural course, health care costs, and quality of life effects with recurrent GIB, as demonstrated in a Japanese study by Aoki. Authors report a cohort of 342 LGIB patients with 19±22 months of surveillance; 19% of patients had a recurrent LGIB at 1 year follow-up and 46% at 5 years, there were 1 to 5 rebleeding episodes per patient (mean 1.7) [18].

In a single-center retrospective study by a Danish university clinic team, where all patients with the diagnosis of GIB in 2012 were examined, application of antithrombotic therapy was reported but not analyzed in a subgroup [13]. The main outcome of that study was an unexpectedly low rate of adverse events (5% GIB) reported to the local Health and Medicines Authority, which shows that a registry study alone cannot be a sufficient source of post-marketing NOAC adverse events statistics.

A large prospective cohort study of NOAC-treated patients in the administrative district of Dresden included over 4000 patients [3, 4]. The patients were enrolled from over 230 physicians' offices and hospitals. The main focus of this study was the prospectively collected data on therapy complications with focus on bleeding events and therapy discontinuation.

Clinical outcomes, such as mortality, hospitalization rate, therapy adherence and thromboembolic events, were systematically analyzed. There were however little data describing GIB treatment or patients' individual comorbidity burden. Study population of the Dresdner NOAC registry consisted initially only of patients receiving NOACs, later it was expanded by inclusion of those receiving VKA. The proportion of individual NOAC-substances is provided in the following part.

Some studies on GIB are based on endoscopic protocols [20, 85, 87], others - on patients' diagnoses submitted at discharge [8, 17, 82]. For the present study we chose the per-protocol design to make sure the GIB diagnoses are accurate, since endoscopy is the first and standard imaging and treatment option in GIB nowadays [27, 88]. Most surveys included both, patients who were admitted to hospital and those who were treated in emergency department, and were discharged on the same day without endoscopic examination or directly after it. In a 2004 Canadian study 11.7% of patients had their UGIB treated with an upper GI endoscopy as outpatients [16]. A nationwide 2011 UK study included 26% participants with UGIB, who did not undergo any endoscopy at all during their hospital stay [17]. In an LGIB trial 6,9% of patients had a recurrent LGIB and were treated for it without hospital admission [42]. In the present study sample, only patients who had endoscopic examination or were assigned for it were included. Based on the knowledge of the clinic practices, we can ascertain that every patient with GIB signs or symptoms was offered endoscopic examination. There were cases though when the suggested endoscopy was declined (e.g. in terminally ill of fragile and elderly patients). Such cases were not recorded and are beyond the scope of the present study. In the present study, only in 2 out of 803 GIB cases endoscopic examination was not performed. Modern trend of performing endoscopic examination of all patients with GIB was noted in a review of GIB epidemiology as an accomplishment in modern medicine [21].

10.2. Study group characteristics

This study was performed to acquire the so called "real-life data" collected in a medium-sized rural hospital, as opposed to high-volume clinics evaluated in prospective and retrospective multicenter trials. The present retrospective study included 830 patients eligible for the analysis, 57% of them were men and 43% - women with the mean age of 72.6±15.1years, ranging from 20 to 98. The mean age is comparable to Phase III NOAC studies, where the mean age was 71 [49]. In the US American NOACs versus VKA studies based on insurance claims registry, patients were younger on average: 57.6±13 [63] and 67.0±11 [78] years old, respectively, burden of

comorbidities in the least two studies was also significantly lower (45.9% had CHADS2 Score 0-1 [78] compared to only 17% in the Phase III NOAC studies).
24.2% of the presently examined patients with GIB received OAC, either VKA (13.8%) or NOACs (10.4%). The prevalence of OAC therapy in the present study was higher than in some previous population-based GIB trials, where 7%-11% of UGIB patients were taking VKA in years 1999-2002 [14, 16, 17]. In more recent single-center trials, proportion of VKA-treated patients was 10%-24% in UGIB, and 7%-29% in LGIB during the period of 2004-2013 [18-20, 42, 89].

10.2.1. Indication for OAC

Main indications for OAC were atrial fibrillation (80,1%) and venous thromboembolism (15,9%). Depending on study settings, the proportion of patients with mechanical heart valves may vary largely. Thus, in the present study of predominantly rural population, it was very low – 0.4% of patients (n=3), while in the 2005 study in the administrative district of Dresden, where both rural and urban population was included in the multicenter study (21 hospitals), the prevalence of mechanic heart valves as an indication for VKA therapy was 11.4% (n=33) - at least ten times higher than in the present study [68]. In a single-center study in Rochester (USA), 4.2% of patients had mechanic heart valves at the time of GIB [90], in a single-center GIB study in Boston (USA), the prevalence of mechanic heart valves was about 9% [15]. In a single-center retrospective study of patients with supratherapeutic INR values, 37% of patients had mechanic heart valves, which was not observed in any other population-based study [23].

10.2.2. Comorbidities

36.0% of patients included in our study suffered from diabetes, 29.9% had ischemic heart disease, 14.9% had malignant disease, 13.5% had liver cirrhosis. Outcomes of GIB is undoubtedly dependent on confounders, such as underlying diseases. Only 36.4% of the study population had none of those comorbidities. Ischemic heart disease and diabetes mellitus (type I or II) were significantly more often seen in the group receiving VKA and NOACs. A direct comparison of CHADS2/ CHA_2DS_2-VASc Scores is not possible with current study data. Spectrum and prevalence of comorbidities in current study was comparable with this from study of VKA-associated bleedings by Halbritter in the same geographical district in 2005, the investigators reported DM in 29.3%, ischemic heart disease – 29.3%, whereas other comorbidities were significantly lower: malignancy 4.5%, liver cirrhosis 1.7%, GIB in the past medical history 3.4% [68]. Variance of comorbidities was very high among trials' participants, illustrated by DM prevalence (12-40%) [1, 42, 55, 58] or malignant disease (4.5% to 23%) [17,

42, 68, 82]. Risk stratification with CHA_2DS_2-VASc and HAS-BLED Scores was developed to attenuate these differences and help during patients enrollment and study results comparison. The proportion of patients referred to hospitals from nursing facilities in the present study was 14.2%, in an national-wide British UGIB trial 2.8% patients were residents of a nursing care [17]. This is hard to compare with many other GIB studies, because that kind of information was rarely reported and was used as exclusion criteria in some VKA/NOAC studies [19, 78].

10.3. Utilization of anticoagulant drugs

The proportion of VKA and individual NOAC substances in the present study was as follows: 30% rivaroxaban, 7% dabigatran, 5% apixaban, 57% VKA. In a study by N. Sengupta in 2014 that proportion was: 6% rivaroxaban, 6% dabigatran, 1% apixaban, and 74% for VKA, respectively. The remaining 14% were treated with parenteral heparin because the study was not limited to OAC and also included GIB among already hospitalized patients [15]. In a registry-based US study, the prevalence of VKA was 86%, whereas rivaroxaban was 4% and dabigatran 11% [63]. Distribution of anticoagulants might differ largely dependent on national and regional practices. There was no reliable data available on head-to-head comparison of different NOACs with each other at the time when the present study was performed. In 3 out of 201 cases (1.6%) a repeated GIB occurred initially during VKA therapy and the second time as VKA was switched to rivaroxaban. There were no data available on how many patients changed or discontinued their VKA/NOAC therapy after hospital discharge. However, others reported that as much as 15% of rivaroxaban users discontinued their therapy in the first year due to side effects [91]. Observation studies have shown that discontinuation of either VKA or NOACs was associated with increased rate of thromboembolism and overall mortality. Resuming the treatment after hospital discharge did not result in significant increase in the rate of recurrent GIB in observational prospective studies, although this effect was not tested in randomized controlled trials [15, 92].

There were 73 patients (9.8% of the total number of patients – not cases) with more than one bleeding event within the study period; 6 patients out of 73 had at least one recurrent GIB event at the time of treatment with OAC and then again after OAC suspension.

10.4. Localization of bleeding lesions

A bleeding event was included in the present study, only when confirmed/witnessed by a member of the medical or nursery staff, an objective rule used in a study by A. Barkun [16]. All the observed bleeding events can be classified, according to broadly used ISTH classification, as “major bleeding”, since they were all overt GIB [84]. There were 55.2% of UGIB, 42.5% of

LGIB in the present study population. Among patients not taking OACs the proportion of upper and lower GIB was ca. 60%:40%, whereas among patients taking VKA and NOACs upper and lower GIB events occurred in ca. 50%:50%. According to classical textbooks, the prevalence of upper and lower GIB in general population is approximately 80%:20% [5, 7]. In two US community-based cohorts from 1996-2009, with 54-58% of patients taking VKA, a similar proportion of UGIB (49%) and LGIB (23%-27%) was observed. Remarkably as many as 26% of patients from that report were classified as "GIB of unknown source" [82]. In a population-based study in the administrative district of Dresden (which encompasses the catchment area of the present study), only VKA-treated patients were studied and the proportion of UGIB/LGIB was 75% vs.25% in 2005 [68]. In a 2013 analysis of patients with GIB requiring ICU treatment the UGIB/LGIB proportion was also 75% vs. 25% [89]. A significant variation (up to 4.5-fold) in the reported annual incidence of LGIB in population should not be forgotten when analyzing the relative rate of UGIB/LGIB [18, 46]. There are also reports stating a rising frequency of LGIB [45], which in some study settings was even more common than the UGIB [12].

The origin of GIB remained unknown or the diagnosis was uncertain in only 1.5% of present UGIB cases (n=7) and in 18.4% of LGIB cases (n=65). Among those cases, 2 out of 7 UGIB cases were reported in patients on OACs (one treated with VKA and one with dabigatran). For LGIB the proportion was completely different: 15 and 19 patients received VKA and NOAC, respectively, resulting in 52.3% of anticoagulated patients in the group of uncertain diagnoses.

A high percentage of unclear LGIB sources was described in many studies, e.g. 30% by Sengupta et al., with VKA prevalence of 20% and NOACs of 8% in the whole study group [42]; 30%-43% of unknown LGIB sources were described by Rubin et al., where only patients receiving VKA were included [23]. 18% of LGIB with unknown source was described in a study of ICU-patients in Aachen, Germany [89]. At the same time, some studies reported much lower rates of unknown LGIB events, e.g. 2.6% in a Japanese study [18]. Lack of knowledge about the pathogenesis of many LGIB cases is a matter of major concern in modern gastroenterological society [42, 46].

In large-scale clinical trials, the Dieulafoy′s lesions are reported in 1%-5% of cases [15, 20, 89]. This type of bleeding lesion was not recorded in the present study at all. It could possibly be responsible for some events with unclear source because of its brisk pattern of active bleeding. In the cases of endoscopically examined bleeding under the present survey, the endoscopist was not expected to define the bleeding source in ambiguous situations, but a ward physician, who wrote the discharge documentation, was responsible for the diagnosis.

10.5. Treatment of GIB

There is a well-established consensus about treatment of acute UGIB, recommended in current guidelines, which are applicable to the patient groups receiving OAC [5, 22, 27]. Presence of OAC did not affect the choice of GIB treatment modality, as reported in studies on patients receiving OAC and OAC naïve [15, 23, 24, 40]. For this group of patients, conventional endoscopic methods of GIB treatment are recommended [71, 93].

10.5.1. Pharmacological therapy

There is a general recommendation to substitute Vitamin K to correct supratherapeutic INR values (INR>3.0) before endoscopy is applied, because it may facilitate endoscopic treatment, although prospective data is lacking [22]. It was not possible to estimate the utilization of vitamin K therapy in the present study because of its retrospective design and the lack of documentation, although a high prevalence of its use can be assumed based on the observed INR-dynamic. Administration of vitamin K is a common procedure which could be seen in many trials, e.g. by Rubin et al., where INR mean value in VKA-patients was 1.8 prior to upper GI endoscopy and 1.6 prior to lower GI endoscopy [23]. Other studies report application of vitamin K in 40%-84% of cases [15, 23, 68].

Further medical therapy of GIB in patients treated with OACs, both VKA and NOAC, is the same as in native patients (i.e. neither VKA, nor NOACs). The standard is administration of parenteral PPI for UGIB, and infusion/transfusion of crystalloids, colloids, and blood products. Specific agents that antagonize the effect of NOACs were introduced to the market in 2015 [37, 38], and this new type of treatment modality was not used when the present study was conducted.

If in patients a GIB was diagnosed, OAC therapy was suspended in 100% of cases, as advised by the current guidelines. It is worth noting that in a multi-center population-based UK study, VKA therapy was not suspended in 13% of acute UGIB cases [17]. In the present study, patients who had mechanical heart valves were treated with aPTT-controlled intravenous heparin, which is approved by current guidelines [94]. There is growing evidence that an early restart (2 weeks after the bleeding event) of VKA/NOAC therapy is quite safe [15]. A 2015 study showed that the restart of OAC therapy reduced mortality and did not raise rebleeding rates [92]. In our retrospective study, no data on VKA/NOAC restart in patients after discharge were available.

10.5.2. Utilization of blood products

The comparison of number of RBC and FFP units transfused to patients in VKA/NOAC groups did not yield statistical significance: 41.7% vs. 46. 5%. These patients received 3.9/3.6 (mean)

units of RBC. 7.0% (VKA) vs. 9.3% (NOAC) and 2.3 vs. 2.8 units of FFPs. Patients included in the present study received comparably less blood product transfusions than in many other published GIB series. In a survey comparing patients with normal INR to those with VKA-related INR≥1.3, mean of 6.6 and 9.1 RBC units were transfused, respectively [20]. In a study of GIB in the setting of supratherapeutic VKA-induced INR values (INR≥3.9 vs. INR≤3.9) mean 3.9 RBC units were transfused to 75% of patients in both groups [23]. FFP was transfused to 73% patients in that study [23]. In a 2005 survey, encompassing the same geographical region as in the present study, only VKA-treated patients were included: 48% of UGIB and 37% of LGIB received RBC, 8%-11% received FFPs, and 5%-19% received PCCs [68]. In another study, 63% of patients, while on VKA, NOACs, or heparins, received RBC, and 38% of them FFPs [23]. In a recent study testing the restrictive vs. liberal transfusion rule in acute UGIB, mean of 1.5 and 3.7, RBC units were transfused to 49% and 86% of patients, respectively [33]. The Dresden NOAC register study group, when presenting the outcomes of rivaroxaban use [4], reported low utilization of RBC (6.1%) and (FFPs 9.1%) in major bleeding events (ISTH definition [84]). At the same time, PCC utilization in the same group was with 9.1% relatively high. An endoscopic examination or surgery was performed in only 38% reported of major bleeding cases, with GIB among them, the rest cases were treated with compression, tamponade, transfusion or watchful waiting [4]. In a community-based study, where cardiologic patients with >50% VKA treatment rate experiencing “major GIB” were included, a surprisingly high (96%) rate of RBC transfusion was reported [82]. It should be noted that the definition for “major GIB” in that study was either RBC transfusion or a fatal outcome, which differs from the modern ISTH definition [84].
In life-threatening GIB, a substitution of clotting factors with PCC and FFP is considerable [4, 24, 51, 89, 93]. In the present study, 4.7% of patients with NOAC therapy received PCCs, compared to 7.8% in the VKA group and 4.0% in the native group.

10.6. Endoscopic studies and therapy

Current population-based studies show a decreasing rate of admission for peptic ulcer disease [9], which was due to implementation of prognostic scores allowing outpatient treatment for selected patients with a low-risk peptic ulcer disease [5, 27, 95]. 99.8% of our study patients received at least one endoscopic examination. There are retrospective studies with high proportion of patients not receiving any endoscopic evaluation for GIB episodes during the index hospitalization, ranging from 4.7-50% [9, 17, 23]. However, the endoscopy was performed later as an outpatient procedure.

10.6.1. Endoscopic interventions

In our study records, there were 67% elective and 33% urgent endoscopic examinations. 85% of urgent and 7.1% of elective procedures were performed on the day of the admission (GIBs developed in hospital were not counted), which closely corresponds to 76% of endoscopic examinations within 24 hours from admission in another UGIB survey [16]. In 21.8% of GIB events in the present study, endoscopic therapy was applied. There were 16.5% of interventional endoscopies in the VKA group and 20.9% - in the NOAC group. Among UGIB cases, there were 18% and 23% of interventional endoscopies in VKA and NOAC groups, respectively; in LGIB cases, that proportion was 16% and 20%, respectively. In non-anticoagulated patients, a similar rate of interventional upper GI endoscopies was observed with 27.7% (χ2-test p=0.23), whereas interventional lower GIT endoscopies had the same rate of 16%. The number of therapeutic endoscopies in UGIB studies varied from 7.2-14.7% [23] to 37% [16]. In LGIB studies endoscopic interventions ranged from 5% to 17% [23, 42].

In the present study, the therapy received by patients with UGIB was predominantly adrenalin injection (43%), ethoxysclerol injection (19%), clipping (15%), and polypectomy (15%). There was no significant difference in utilization of a single therapeutic method between VKA/NOACs groups. The same modalities were reported in GIB studies in patients treated with VKA [20, 89] even when they were having supratherapeutic INR values [23].

10.6.2. Endoscopic treatment success

Treatment of GI bleeding in patients on VKA/NOAC in the present study was effective in 97.6% of cases, recurrent bleeding was observed in 6.6% of cases. Surgical treatment of GIB was rare (2.3% of cases) and performed in recurrent or profuse and otherwise uncontrollable bleeding. Primary endoscopic treatment showed similar efficacy in patients taking VKA/NOAC in comparison to non-anticoagulated patients, 98% and 99%, respectively. Endoscopic treatment failed in 1.8% of cases: 15 cases, including one treated with NOAC and one with VKA. Among few patients in whom bleeding could not be controlled with endoscopic procedure, mortality rate reached 60%. In a study of UGIB in the presence of VKA, a comparable 98.8% of endoscopic treatment success rate was reported [20]. In a study with LGIB patients, 4.4% of persistent bleeding was observed, leading to subsequent surgery [42]. A much higher rate of endoscopically uncontrollable UGIB (10.2%) and uncontrollable LGIB (10.6%) was reported in a study from Aachen, where only patients from an ICU were enrolled [89].

10.7. Surgery

Surgery was performed in 2.3% of cases, mortality rate in operated patients was 26%, which reflects the severity of the disease requiring surgery. There was no difference in need for surgery

between VKA and NOAC patients: 0.09% and 2.3%, respectively, and very few surgeries were recorded (2 and 1 surgeries in the VKA and NOAC subgroups, respectively).
Some studies reported higher operation rates, 2%-6% [33], 6.5% [16]. In surveys with the focus on VKA therapy, the operation rate did not depend on INR values on admission: 2.9% for INR≥1.3 and 7.6% for INR<1.3 [20]; in cases of supratherapeutic INR, operation rates were 1.8% and 2.3% for INR ≥4 and INR<3.9 [23], respectively. The need for surgery was very similar in patients with GIB admitted of the hospital and in in-patients: 6.4% vs. 6.5% [14]. According to a large 2007 British population-based study, mortality of patients operated on for UGIB was 30% [17]. Others reported lower mortality rates: 5.4% and 8,0% within 30 and 90 days after the surgery, respectively [15, 16].

10.8. Recurrent GIB

73 patients (9% of all cases) had recurrent bleeding events during the study period. Proportion for UGIB/LGIB was 7.2% vs. 5.4% (p=0.3 using χ^2). A median of 2 GIB events per capita and a maximum of 5 GIB events were recorded. The comparison of cases with and without OAC has shown that the use of any OAC before admission, either VKA or NOAC, did not increase the rate of recurrent bleeding - either during hospital stay, or within 30 days after the discharge. Recurrent bleeding rates in VKA and NOAC patients were statistically not significantly different; 2.6% vs. 8.1% for rebleeding within the same hospital stay, and 4.3% vs. 2.3% for rebleeding within 30 days of discharge. Recurrent GIB in the OAC-naïve group was 7.2% during hospital stay and 3.2% within 30 days of discharge.
Some researchers emphasize the negative effect of readmission to hospital for any reason and not only for recurrent GIB within 30 days after the discharge since it affects the quality of life and depletes healthcare resources [18]. In the present study a recurrent GIB led to readmission within 30 days in 3.3% of cases, whereas other than GIB indications constituted 9% of cases, thus being 3.6 times more common. There was no difference in recurrent hospitalization rate between groups of UGIB/LGIB, or VKA/NOAC/naïve. A single-center LGIB study showed that 21% of patients were readmitted within 30 days, 1/3 of them for recurrent GIB and 2/3 - for other conditions (volume overload, infection, thromboembolic events, etc.) [42]. According to a multi-centre trial, rebleeding rate for UGIB within 30 days after the hospital discharge was with 0.8% much lower [16].
Other studies reported similar data that VKA therapy at the bleeding episode did not lead to higher rebleeding rate during hospital stay; it was 13% in both VKA and naïve patients in a UK population-based study [17]. Rebleeding rate in patients with supratherapeutic INR (at

admission) was not different from that observed in the group with therapeutic INR-values (5.5% vs. 4.7%) [23]. When only patients admitted to ICU were analyzed, rebleeding rate was similar to those reported in other less focused studies, 10.8% for UGIB and 10% for LGIB; rebleeding was not associated with the use of OAC therapy (odds ratio 95% CI: 0.25-1.66) [89].
In the present study, the rate of recurrent bleeding was the same in patients receiving single or double antiplatelet therapy or none (6.8%, 5.9%, and 7.5%, respectively). NSAIDs were used by 7.5% of the study population and 35.1% received at least one antiplatelet drug (mostly aspirin). The rate of recurrent bleeding did not differ between users of these medications and in patients not taking them. According to a 2007 population-based study of UGIB in Great Britain, 11% of patients with UGIB were taking NSAIDs (28% was aspirin) and the recurrent bleeding rate was similar in patients receiving antiplatelets, or NSAIDs, or none of these [17].
If only LGIB events are taken into account, the recurrent bleeding rate within 30 days after the discharge in the present study is the following: 1.9% in the naïve group, 2.2% in the NOAC group and 8.0% in the VKA group ($p=0.03$, χ^2 for comparison VKA vs. native). There was only one recurrent LGIB in the NOAC group in the present study. A higher rebleeding rate in the VKA group was also reported in a LGIB study, with the rate of 7% within 30 days after the discharge [42]. According to that trial, the use of VKA was an independent and significant risk factor for rebleeding (hazard ratio of 2.9). It is worth noting that the authors reported additional 7% of recurrent LGIB events, which were classified as "minor events" not leading to hospital admission and treated in an emergency room. Another long-term LGIB study (mean 19 months, study duration over 9 years) reported high LGIB recurrence rate: 5% of rebleeding within 1 month after the initial event and 19% within 1 year, 46% of recurrent LGIB within 5 years. Among them over 60% of patients had more than one rebleeding event. Among risk factors for recurrent LGIB, was the use of NSAIDs and aspirin, but not VKA according to the authors' conclusion [18]. In another study in patients treated with VKA and NOACs (all together 33% of all included patients) a 2-years follow-up after the initial GIB and resuming OAC yielded a cumulative risk of 11.1%-13.1% of recurrent GIB [92].

10.9. Restarting systemic anticoagulation after GIB

The present study design could not provide information on whether and when VKA/NOAC therapy was resumed, and whether the resumption of OAC had any effect on rebleeding. In a prospective observational trial [15], restarting systemic anticoagulation after initial GIB did not lead to higher recurrent GIB rate within 90 days of discharge; recurrent GIB were recorded in 14% of patients. At the same time, patients with non-resumed anticoagulation from the same

study had significantly higher rate of thromboembolic events. Notably, rebleeding occurred within 12-13 days (median value) after the initial GIB in both VKA and NOAC groups - with resumed or suspended OACs, whereas thromboembolic events occurred predominantly within 10-30 days [15]. In a 2015 high-powered nation-wide observational trial, patients with atrial fibrillation who developed GIB while taking antithrombotic therapy were included, 44% of them were taking OACs alone or in combination with one or two antiplatelet drugs [92]. It was revealed that 33% of patients restarted OAC therapy after the initial GIB, and among them the risk of recurrent "major GIB" was increased. Meanwhile the risk of developing GIB of any kind was similar in groups of resumed and non-resumed OAC therapy, as a whole, there were about 12% or recurrent GIB in two years of observation. The study raised the problem of determining the appropriate time point to re-start antithrombotic therapy [71, 75, 83].

10.10. Mortality rate

Hospital mortality rate was 3.6% in both VKA and NOAC groups, which was statistically significant lower than 7.9% in non-anticoagulated patients. Mortality 30 days after endoscopy was 5.5% and 4.9% in the VKA and NOAC groups, respectively, and 9.2% in the naïve group ($p>0.05$ for three-way comparison, Pearson χ^2). Mortality rate in the present study is comparable to other published trials.

In two large population-based surveys of UGIB, hospital mortality rate was 7.4% [17] and 5.4% within 30 days after the discharge [16]. Mortality rate within 90 days after the discharge in the patients group treated with VKA or NOACs was 8%, and there was no difference in patients with resumed and suspended anticoagulation [15].

In large community-based retrospective cohorts of cardiologic patients (1996-2009) with 54%-58% prevalence of VKA therapy, mortality rate within 30 days after the discharge was 11-13% [82]. In some groups of patients (age over 85 years) the use of VKA was surprisingly associated with significantly lower mortality. The authors suggested that VKA therapy was more likely to be administered to healthier patients – a typical bias seen in non-interventional studies, possibly in the present study as well. The conclusion made by the authors was that GIB in patients treated with VKA was at least not worse in outcomes compared to non-VKA patients [82]. In a 2014 study of rivaroxaban-associated major bleeding events (according to ISTH definition, other sources than gastrointestinal were also included) mortality was 5.1% by day 30 and 6.3% by day 90 after the initial bleeding [4]. In comparison, the 2005 study in the same area (Dresden region), reported 14.1% 90-day mortality for all VKA-associated bleeding events [68]. Dr. Beyer-Westendorf et al., concluded that rivaroxaban was at least not worse than VKA in the "real-life"

setting [4], which corresponds to the results of a randomized controlled phase III ROCKET-AF trial [58]. In a retrospective analysis of ICU-patients suffering from GIB, the presence of VKA/NOAC at admission was a factor significantly associated with better survival in cases of LGIB and UGIB: 3.6% and 2.9% vs. 17.2% and 14.9%, the latter numbers referred to patients without OAC [89]. Another study has shown that the presence of VKA even in supratherapeutic INR values did not lead to higher mortality rate in GIB patients (2.3-7.3%) which is comparable to other studies [23].

An ominously higher mortality rate of 34.5%, according to the present research, was seen among patients with UGIB who developed a recurrent bleeding during the same hospital stay, compared to 4.4% mortality rate among those who did not. The role of underlying diseases, decompensation of comorbidities was often emphasized in reviews, whereas mortality through GIB (fatal blood loss) is becoming rare [5, 18, 20].

Among variceal UGIB with recurrent bleeding, mortality rate was 85.7% compared to 27.1% in non-variceal recurrent UGIB. When analyzed separately, the cases with recurrent LGIB had 15.8% mortality rate compared to 3.0% mortality in LGIB cases without rebleeding. Only 2 patients who received VKA and NOAC (one each) suffered from recurrent bleeding within the index hospital stay and died; further subgroup analysis was not possible because of the small sample size.

A negative prognostic value of recurrent UGIB was stated in other studies and reviews, odds ratio for fatal outcome were 4.2 and 7.3 in two UGIB trials [14, 89]. In a contemporary US textbook, this OR was postulated as high as 10 [5]; the present study confirmed the unfavourable prognostic value of recurrent UGIB.

Our observation reveals that recurrent LGIB is significantly associated with higher mortality, in accordance with a 2008 review by Strate et al. [96]. However, other reviews and guidelines focused on LGIB did not describe this association [5, 88, 97].

10.11. Occurrence of GIB at sub-, supra-, and therapeutic INR ranges

High INR is associated with a higher risk of bleeding [7], as soon as stochastically happening mucosal or deeper lesion becomes an apparent event of bleeding and in that way clinically relevant [24]. In the present study, VKA-treated patients with different INR values were classified as subtherapeutic (17%), therapeutic (33%), supratherapeutic (60%) using common 2.0 and 3.0 cut-off values. All these patient subgroups had comparable rates of mortality, recurrent bleeding, shock at presentation, active bleeding during the endoscopy, need for endoscopic therapy, or the rate of uncertain diagnoses. There was a clear trend towards more frequent UGIB,

as compared to LGIB in patients with higher INR values: 26.74% (INR<2); 42.53% (INR 2-3) and 68.26% (INR>3) (p=0.003, Pearson χ^2). More patients with higher INR values needed RBC transfusions; however, the mean number of RBC units transfused was not higher: 4.4 (INR=2.0-3.0) and 3.7 (INR>3). In a comparator study with supratherapeutic vs. therapeutic INR values, a mean of 3.9 RBC units were transfused per a GIB episode in both groups [23]. In the present study, statistically significant higher mortality rate was observed with higher INR values, when INR was treated as a continuous variable, although there were only 2 fatal outcomes in the group of VKA-treated patients, which limits the validity of this result. In the comparator study, mortality and the need for surgery did not differ between the groups with different INR ranges. Certain selection bias should be acknowledged, because the cited study was performed in a US Veterans Hospital and included 98% of elderly men [23].

The proportion of patients receiving VKA therapy and having subtherapeutic INR values when GIB occurred was 17% in the present study, and 19-26% in other studies [23, 68]. Percent of patients in supratherapeutic range is less comparable between studies since definitions vary. According to authors, 37.2% - 55% of patients had supratherapeutic INR values when the bleeding event occurred [23, 68]. In a multicenter population-based UGIB study from the UK, a 30% prevalence of INR≥5 was stated in 2007, yet no separate analysis of that group of patients was made [17].

4 patients receiving rivaroxaban in the present study had also elevated INR ≥2, although INR is not suitable for therapy control in NOACs [50]. In 5% of all cases, patients with advanced liver failure had INR ≥1.3 and in 1% (n=6) had INR>3.0, however, they were not included in analysis because of a completely different pathogenesis of coagulation defect.

10.12. Occurrence of GIB in thrombocytopenic patients

Thrombocytopenia is defined as platelet count below $150x10^9$/l [7]. In the present study, thrombocytopenia was observed in 9.4% of cases; 63% of thrombocytopenic patients had liver cirrhosis. It is well known that hemorrhagic complications of endoscopic studies are of highest concern if platelets are below $50x10^9$/l [5, 35, 88, 98]. In 1.0% (n=9) of cases in the present study, the platelet count was $<50x10^9$/l. Patients with thrombocytopenia received VKA and NOACs in 12% and 8% (n=8 and n=6) of cases, respectively; a detailed subgroup analysis was not possible because of the small sample size. It is disputable, whether detected thrombocytopenia in the current study should be related to the liver cirrhosis alone or thrombocytopenia should be treated as a result of thrombocytes loss during massive and prolonged bleeding. There was statistically significant higher prevalence of patients with shock

(35.9%) among thrombocytopenic patients (χ2-test, p=0.00001) when compared to patients with normal platelet count.

Thrombocytopenia was an independent negative prognostic factor: mortality rate during hospital stay among patients with thrombocytopenia was 12.8% compared to 5.7% in patients with normal platelet count (and a similar result for 30-day mortality). In contrast to our data, a multicenter study of particularly non-variceal UGIB did not prove a low platelet count as a prognostic factor for mortality or rebleeding [16]. The prognostic value of platelet count could not be separated from the liver disease burden and therefore cannot be considered as a predictor.

10.13. GIB in patients hospitalized for another condition

Patients who developed GIB while being treated in hospital for another medical condition represent 12.0% of the total study population. In a population-based multi-center GIB study, the number of in-patients was 16,4%, which is comparable to our results [17]. There were 25% in-patients included in a nation-wide trial that analyzed the role of PPI in prevention of dabigatran-related GIB [99]. In a study of LGIB, only 10% developed bleeding while being hospitalized for a bleeding-unrelated disease [42].

The in-patients with other bleeding-unrelated diseases had much worse outcomes than those who were treated in hospital primarily for GIB. Hospital mortality in the present study was 21% compared to 4.4% for GIB developed outside of the hospital, 30-day survival was also worse for GIB among in-patients. Exceptions among the in-patients having GIB were those with bleeding after endoscopic interventions, i.e. iatrogenic GIB – there were zero fatal outcomes in that subpopulation (n=13 of 100 in-hospital GIB events). It is known that patients with GIB who were hospitalized for a co-morbidity have a poorer prognosis [5, 9]. In a focused analysis of in-hospital UGIB, mortality rate was reported to be 3 times higher (11% vs. 3.5%). A longer hospital stay and a longer waiting time to undergo the first endoscopy were recorded; the rate of rebleeding or the need for surgery did not differ (13% vs. 15% and 6% vs. 7%, respectively) [14]. There was a lower rate of VKA and NOAC therapy among patients who developed in-hospital GIB (11% compared to 26%). A possible reason is that VKA/NOAC therapy was suspended and bridged with heparins in many cases (mostly before and after surgery). Further analysis of heparins utilization and their impact on GIB was not possible due to the design of the present retrospective study.

10.14. Validity of follow-up using hospital database only

Patient-centered design of the present study allowed a non-interventional follow-up using hospital internal database. The study clinic is in the center of a municipality and the two neighboring clinics share common electronic database.

Only GIB events that led to referral to hospital could be detected and recorded using the present study design, although based on our knowledge of local practices, even minor GIB events were referred to hospital for further evaluation, thus very few patients were not covered by the study protocol.

A US LGIB study reports on a routine telephone check 30 days after the discharge. 14.7% of 271 patients had recurrent LGIB, among them 7.7% were readmitted, 1.8% were treated in the emergency room as outpatients; the remaining 5.2% did not require any medical care because the recurrent LGIB was self-limited [42].

The Dresden NOAC cohort study utilized a prospective design with telephone visits to collect data on NOAC therapy complications. In a report on rivaroxaban, all bleeding complications were reviewed [4]. It was determined that 59% of them were “minor bleeding” not leading to physician contact, over 90% were “non-major bleeding”, according to ISTH classification [84]. 6.1% (3.4 events per 100 patient-years) of all events were “major bleeding” that required surgery or intervention in 2 out of each 5 cases, whereas 3 out of each 5 cases received only RBC transfusion; case fatality is reported at 5.1% by day 30. Compared to that trial, we had 97.7% “major bleeding” events, because it was either “bleeding into critical site, overt GIB” or “bleeding leading to RBC transfusion, death”, according to ISTH classification [84].

For the reason that the number of patients in the catchment area who received VKA or NOAC treatment was not recorded (a study design limitation discussed in a single-center prospective study conducted in Denmark [13]), it was not possible to quantify the risk of GIB in relation to this treatment.

10.15. Past medical history of GIB and PPI use

22.7% patients with recorded GIB cases in the present study had already had a GIB event in the past medical history. This proportion was 14% and 20% in patients with/without VKA in a study of UGIB [82]; 10% of patients developed GIB in hospital and 22% of newly hospitalized for GIB had had a GIB event in the past medical history [14]. It is noteworthy that some investigators excluded patients with GIB in past medical history or patients with recurrent GIB from their studies [8, 63].

In the present study, the rate of PPI intake among patients with GIB in past medical history was higher than among patients with first GIB event, 53.7% vs. 22.5%. The presence of either VKA or NOAC therapy was another factor significantly associated with the higher rate of PPI intake: 36% and 42% for each substance group compared to 27% in the native group (p=0.008 Pearson $\chi 2$). The retrospective design of the present study provided no information on whether previous GIB events were peptic or non-peptic, even upper and lower GIB events could hardly be distinguished based on the medical records alone, nor were there enough data to establish if a patient was receiving an OAC at the time of that historical bleed. In a Hong-Kong retrospective study that analyzed the role of gastroprotective agents in patients taking dabigatran, 14% had had a GIB event prior to the study; the prevalence of PPI use was 18.3%, whereas the use of H2-blockers was 40%, and both medications were associated with protective effect against GIB [99]. The prevalence of PPI intake was 11.3% in UGIB and 16.6% in LGIB patients [45], and 12.7% in a cohort with only VKA or dabigatran patients [1]. In a pan-European pharmacologic study, the prevalence of PPI intake among patients who had an UGIB was 7.3%, although over-the-counter PPIs were not amenable to analysis [76].

10.16. Duration of hospital and intensive care unit stay

There was a mean 8.0±7.8 days duration of hospital stay after the first endoscopic study had been applied, mean hospital stay was 10.1±8.3 days, notably, mean 9.2±7.5 (IQR: 5-11) for new patients and 16.9±10.5 (IQR: 10-23) for patients developing GIB during hospitalization for other conditions. There was no significant difference between native, VKA and NOAC groups. Patients receiving dabigatran had mean of 12.3 days of hospital stay, which is statistically significantly higher than in any other NOAC or VKA group. Currently, we do not have any explanations for the observed longer hospital stay in dabigatran group. Longer hospital stay for dabigatran patients was not reported in phase III and post-marketing studies [1, 55].
Comparable or shorter length of stay in other hospitals with unselected referral was reported: mean 3 days (IQR 1.5-8.5), when only patients treated with VKA were in focus [99], mean of 13±10 days [68], and mean of 8.7 days for both therapeutic and supratherapeutic INR groups [23], mean of 10.6/15.7 days for patients with/without treatment with VKA [20], and 5-6 days in phase III rivaroxaban trial [51].
A significant and expected difference in the length of hospital stay of patients admitted with GIB and those who developed GIB during hospitalization was observed: 5 days (IQR: 2-12) and 18 days (IQR: 8-28) [17], IQR 2-7 and IQR 10-23 days [42], 5.0±5.4 vs. 7.2 ±7.4 [14].

11.7% of patients with UGIB were discharged from emergency department after endoscopic evaluation in the RUGBE trial [16], compared to 2/830=0.3% in the present study.
In the present study, 15.7% of patients needed ICU treatment, with no significant difference between VKA, NOAC and native groups. This is similar to other published data: in a UGIB survey, 16% of newly admitted patients needed ICU stay [14], whereas in another LGIB study 25% patients needed ICU treatment [42]. In the present study, the length of ICU stay was 6.2±7.2 days. In a multi-centre phase III trial the length of ICU stay did not differ between VKA and dabigatran groups and was mean 1.6 vs. 2.7 days according to a published review [51].

10.17. OAC and antiplatelet drugs including triple therapy

The study population included only few patients (n=23, corresponding to 2.7%) with a combination of OAC and an antiplatelet drug. 0.84% of them (n=7) received triple therapy with 2 antiplatelet agents and VKA (n=4), rivaroxaban (n=2) and dabigatran (n=1). The only reliable difference in clinical outcomes was a higher number of RBC units transfused in the triple therapy group; further conclusions were not possible because of the small sample size of group with triple antithrombotic therapy. The clinical outcomes in patients receiving monotherapy (aspirin, clopidogrel, etc.) or a double antiplatelet therapy with two antiplatelet agents, were comparable to those in patients receiving no antiplatelets or receiving only VKA/NOAC. At the same time, the present study design did not provide sufficient ground to estimate the relative risk of GIB with either type of therapy.
There are many other studies reporting a wider use of antiplatelets with OACs. The prevalence of ASA or clopidogrel use with OACs was 29-41% in 4 pivotal NOAC trials as summarized in a meta-analysis [49], it was 31-37% in a nation-wide cohort study in Denmark [1], and approximately 30% in an observational study of dabigatran in Hong Kong [99].
In a large meta-analysis where adverse events of taking aspirin were addressed, 6% of all patients received it as a component of triple therapy, compared to 3.0% in the present study, where only patients with GIB were in focus [73]. The same proportion, 6% of patients, had a triple therapy in a large observational US cohort, where relative risk of adverse events was studied [80]. Thus, complex (double, triple) antithrombotic therapy in the present study is underrepresented compared to more focused studies.

11. References

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12. Affidavit

“I, Smirnov Ivan certify under penalty of perjury by my own signature that I have submitted the thesis on the topic Retrospective study of etiology and treatment outcomes of patients with gastrointestinal bleedings with focus on exposure to vitamin K antagonists and new oral anticoagulants in a community care hospital in Saxony. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (see above) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

13. CV

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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15. List of abbreviations

AF	Atrial fibrillation
aHT	Arterial hypertonia
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AT III	Antithrombin III
AVM	Arteriovenous malformation
BID	bis in die, or “two times a day”
CI	Confidence interval
COX	Cyclooxygenase inhibitor
DM	Diabetes mellitus
EMR	Endoscopic mucosal resection
ERC	Endoscopic retrograde cholangiography
FDA	Food and drug administration
FFP	Fresh frozen plasma
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
GIST	Gastrointestinal stromal tumor
GIT	Gastrointestinal tract
H.pylori	Helicobacter pylori
ICB	Intracranial bleeding
ICU	Intensive care unit
IHD	Ischemic heart disease

INR	International normalized ratio
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
LGIB	Lower gastrointestinal bleeding
LMWH	Low molecular weight heparin
MALT	Mucosa-associated lymphoid tissue
NOAC	Non-vitamin K antagonist oral anticoagulants
NSAID	Non-steroidal anti-inflammatory drugs
OAC	Oral anticoagulants
OR	Odds ratio
PC	Platelet concentrates
PCC	Prothrombin complex concentrate
PEG	Percutaneous endoscopic gastrostomy
PPI	Proton-pump inhibitor
QD	quaque die, or “once a day”
RBC	Red blood cell
RCT	Randomized controlled trial
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitors
TIPS	Transjugular intrahepatic portosystemic shunt
UGIB	Upper gastrointestinal bleeding
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

16. List of Figures, Graphs and Illustrations