THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

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Key Points

- In a real-world setting, annualized bleeding rates of major rivaroxaban bleeding are lower than those reported for vitamin K antagonists.
- Treatment of major rivaroxaban bleeding is simple and rarely requires pro-coagulants; outcome at 90 days is better than that reported for vitamin K antagonists.

Worldwide, rivaroxaban is increasingly used for stroke prevention in atrial fibrillation and treatment of venous thromboembolism, but little is known about rivaroxaban-related bleeding complications in daily care. Using data from a prospective, noninterventional oral anticoagulation registry of daily care patients (Dresden NOAC registry), we analyzed rates, management, and outcome of rivaroxaban-related bleeding. Between October 1, 2011, and December 31, 2013, 1776 rivaroxaban patients were enrolled. So far, 762 patients (42.9%) reported 1082 bleeding events during/within 3 days after last intake of rivaroxaban (58.9% minor, 35.0% of nonmajor clinically relevant, and 6.1% major bleeding according to International Society on Thrombosis and Haemostasis definition). In case of major bleeding, surgical or interventional treatment was needed in 37.8% and prothrombin complex concentrate in 9.1%. In the time-to-first-event analysis, 100-patient-year rates of major bleeding were 3.1 (95% confidence interval 2.2-4.3) for stroke prevention in atrial fibrillation and 4.1 (95% confidence interval 2.5-6.4) for venous thromboembolism patients, respectively. In the as-treated analysis, case fatality rates of bleeding leading to hospitalizations were 5.1% and 6.3% at days 30 and 90 after bleeding, respectively. Our data indicate that, in real life, rates of rivaroxaban-related major bleeding may be lower and that the outcome may at least not be worse than that of major vitamin K antagonist bleeding, and probably better. This trial was registered at www.clinicaltrials.gov as identifier #NCT01588119. (*Blood*. 2014;124(6):955-962)

Introduction

For more than 5 decades, vitamin K antagonists (VKAs) had been the standard of long-term anticoagulation in indications such as stroke prevention in atrial fibrillation (SPAF) and treatment of venous thromboembolism (VTE). Although effective, VKA therapy is complicated because of the significant interindividual variations in metabolism, numerous drug–drug interactions, and the interaction with dietary intake of vitamin K.[1] Therefore, routine monitoring of the anticoagulation intensity is necessary. In daily care, the "time in therapeutic range" of VKA patients is approximately 50% to 70%,[2] which is a clear indicator of the problematic individual dose-finding. As a result, thromboembolic as well as bleeding complications with VKAs are common. The annual rates of major bleeding in VKA patients in daily care are estimated to be up to 8%.[3-8] Furthermore, in cases of major bleeding or bleeding requiring hospitalization during VKA therapy, case fatality rates were shown to be as high as 13% to 18%.[7-9]

The non-VKA oral anticoagulant (NOAC) rivaroxaban is a selective inhibitor of the activated coagulation factor X (factor Xa). It has an excellent dose–response relationship, few drug–drug interactions, and no drug–food interactions. As a consequence, no routine coagulation monitoring is required and patients can be treated with a fixed-dose regimen. Large phase 3 trials in SPAF and VTE treatment compared rivaroxaban with VKA and consistently demonstrated high efficacy and safety for rivaroxaban.[10-12] Major bleeding events were rare in these large phase 3 trials and the rate of intracranial hemorrhage—the most feared complication of anticoagulant therapy—was significantly reduced with rivaroxaban compared with VKA.[10,13]

However, bleeding is the most common side effect of rivaroxaban and, as with VKA treatment, it has to be expected that rates, pattern, and outcome of rivaroxaban-related bleeding in unselected daily care patients may be different from the favorable outcomes seen in selected patients in clinical trials, because patients in daily care more often show significant comorbidities and are treated under a less intensive surveillance.

Because routine coagulation monitoring tests are not generally available for emergency situations during rivaroxaban therapy and specific reversal agents are lacking, there is a general fear that bleeding complications during rivaroxaban therapy cannot be adequately controlled and may result in poor outcomes.

Submitted March 18, 2014; accepted May 14, 2014. Prepublished online as *Blood* First Edition paper, May 23, 2014; DOI 10.1182/blood-2014-03-563577.

The online version of this article contains a data supplement.

There is an Inside *Blood* Commentary on this article in this issue.

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Using data from a large, prospective multicentric NOAC registry, the following objectives were addressed:

- Rates of rivaroxaban-associated bleeding complications in daily care;
- Distribution pattern of minor, nonmajor clinically relevant (NMCR) and major bleeding;
- Management of rivaroxaban-associated bleeding with the focus on surgical or interventional treatment and the use of pro-coagulant therapies; and
- All-cause and bleeding related mortality at 90 days after rivaroxaban-associated bleeding.

Methods

Patients

The Dresden NOAC registry (NCT01588119) is a large, prospective registry in the administrative district of Dresden (Saxony), Germany. In this ongoing project, a network of more than 230 physicians from private practices and hospitals enroll patients treated with a NOAC, who are prospectively followed up by the central registry office. Patients are eligible if the following inclusion criteria are met:

- Planned NOAC anticoagulation for at least 3 months;
- Therapeutic NOAC indication including SPAF, deep vein thrombosis, pulmonary embolism, and other indications;
- Age >18 years;
- Written informed consent; and
- Availability for follow-up by telephone visits.

No exclusion criteria apply. Patients are followed up by telephone visits at 30 days after enrollment and quarterly thereafter to collect data on the efficacy, safety, and management of NOAC therapy in daily care.

Data collection and classification of bleeding complications

During all visits, suspected bleeding events were documented in the case report form and additional data (laboratory tests, imaging results, reports from treating physician, protocols of surgery or intervention, discharge letters, death certificates, and autopsy reports as applicable) were collected for central adjudication and bleeding event classification.

Bleeding management was assessed using patient narrative and all relevant medical documents, including: the objectively documented necessity of interventional or surgical treatment; rates and amount of red blood cell (RBC), plasma or platelet transfusions; or the use of pro-coagulants such as prothrombin complex concentrate (PCC), factor VIII inhibitor bypass activator, or recombinant factor VII concentrate.

Outcome of bleeding event was established for days 30 and 90 postbleeding using documentation of the acute bleeding episode as well as data from the next scheduled phone visits.

Outcome parameters

The primary outcome was the annualized rate of major bleeding. Secondary outcome parameters were as follows:

- Annualized rate of any rivaroxaban related bleeding;
- Annualized rate of NMCR rivaroxaban related bleeding;
- Rates of major cardiovascular events within 90 days after major rivaroxaban-related bleeding;
- All-cause and bleeding-related mortality at 30 or 90 days after major rivaroxaban related bleeding; and
- All-cause mortality 90 days after hospitalization for rivaroxaban-related bleeding.

All bleeding events were classified as minor, NMCR, or major bleeding using the International Society on Thrombosis and Haemostasis (ISTH) definition[14]:

Major bleeding was defined as overt bleeding with any of the following:

- Documented transfusion of at least 2 U RBCs;
- Drop in hemoglobin >2 g/L;
- Surgical revision from bleeding;
- Bleeding into critical site (intracranial, intraocular, intraarticular, retroperitoneal, overt gastrointestinal bleeding); or
- Fatal bleeding.

NMCR was defined as overt bleeding with any of the following:

- Nonmajor bleeding compromising hemodynamics;
- Any bleeding leading to hospitalization;
- Subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause;
- Intramuscular hematoma documented by ultrasonography;
- Epistaxis that lasted for more than 5 minutes, was repetitive (ie, 2 or more episodes of bleeding more extensive than spots and a handkerchief within 24 hours), or led to an intervention (eg, packing or electrocoagulation);
- Gingival bleeding occurring spontaneously (ie, unrelated to eating or tooth brushing) or lasting for more than 5 minutes;
- Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (eg, catheter placement or surgery) of the urogenital tract;
- Macroscopic gastrointestinal hemorrhage, including at least 1 episode of rectal blood loss, if more than a few spots on toilet paper;
- Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism; or
- Any other bleeding type considered to have clinical consequences for a patient such as medical intervention; the need for unscheduled contact (visit or telephone call) with a physician, temporary cessation of a study drug, or temporary cessation of a study drug; or associated with pain or impairment of activities of daily life.

Minor bleeding was defined as every overt bleeding event that does not fulfill the criteria of major or NMCR bleeding.

Major cardiovascular events were defined as fatal or nonfatal cardiovascular complications events consisting of centrally adjudicated events as follows:

- Acute coronary syndrome, including unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction;
- Stroke or transient ischemic attack or systemic embolism;
- Deep vein thrombosis or pulmonary embolism; or
- Any other fatal cardiovascular event.

Outcome of bleeding complications

Mortality rates after rivaroxaban-related bleeding were assessed at days 30 and 90 postbleeding. Furthermore, for comparison with available data for VKA-related major bleeding (often defined as bleeding leading to hospitalization),[7,9] the case fatality rate (all-cause mortality) of all rivaroxaban bleeding events leading to hospitalization was evaluated.

At days 30 and 90 postbleeding, patients were also evaluated for suspected major cardiovascular complications after the acute bleeding event. For this, results of imaging, laboratory tests, patient charts, discharge letters, autopsy reports, and death certificates were reviewed and categorized using standard definitions.

Statistics

Two different sets of analyses were performed:

1. Rates of bleeding complications (all, major, and NMCR bleeding) during rivaroxaban therapy were evaluated in the valid-for-safety analysis. All patients enrolled in the rivaroxaban group (consisting of SPAF and VTE patients) were included, but only bleeding events that occurred during

rivaroxaban treatment or within 3 days after interruption or discontinuation of treatment were evaluated. Therefore, bleeding events occurring during temporary rivaroxaban interruption (>3 days after last intake) were excluded from analysis. Patients with permanent discontinuation of rivaroxaban were censored at day 3 after last rivaroxaban intake. Bleeding rates were separately calculated for VTE and SPAF patients. Patients who experienced new onset of VTE with a history of SPAF were included in the VTE cohort and vice versa, depending on the current indication for rivaroxaban use.

2. Pattern, management, and outcome of rivaroxaban-associated bleeding were evaluated in the as-treated analysis. In contrast to the valid-for-safety analysis, this analysis included all bleeding events occurring within 3 days after the last intake of rivaroxaban in any registry patient and also included events in patients who were enrolled on anticoagulants different from rivaroxaban and were switched to rivaroxaban during the study period before the respective bleeding event occurred.

For comparison of means, a *t* test for independent samples was performed. For comparison of medians or frequencies, Kruskal–Wallis test or χ-square test was used, respectively.

The 95% confidence intervals (CIs) of proportions are calculated according to the Clopper-Pearson method.

Data are presented as absolute and relative frequencies, mean and standard deviation, or median with interquartile range as difference between 25th and 75th percentile, where appropriate. All *P* values presented are exploratory in nature; thus, no adjustment of type 1 error for multiple testing is conducted. A *P* value below .05 was considered to be statistically significant.

Event rates were calculated as events per 100 patient-years with their 95% CIs. Here, the following formula is used:

$$\text{Event rate} = \text{number of events}/\text{total time under risk}.$$

Total time under risk is the sum of all days from inclusion to the registry until day of first event divided by 100×365 days and has 100 patient-years as the unit. Corresponding CIs and *P* values are calculated using the Poisson distribution.

All statistical analyses were carried out using the IBM SPSS Statistics Version 19, Statistical Analysis System Software Version 9.3, and R (Comprehensive R Archive Network).

Ethics

The study protocol of the Dresden NOAC registry was approved by the local ethics committee at the Technical University Dresden (AZ EK 349092011) and registered at ClinicalTrials.gov (#NCT01588119). All patients provided written informed consent, including a data protection waiver before enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Results

Cohort characteristics

Between October 1, 2011, and December 31, 2013, 2346 patients were enrolled in the registry. Of these, 1776 (75.7%) received rivaroxaban: 1200 (67.5%) for SPAF and 575 (32.4%) with VTE. One patient (0.1%) was excluded from analysis because of an off-label indication (peripheral arterial bypass). At baseline, compared with patients with VTE, patients receiving rivaroxaban for SPAF were older (75 vs 68 years) and more often had coronary artery disease (21.8% vs 8.5%) or a history of stroke or systemic embolism (13.9 vs 6.3%), each of which was statistically significant. Further baseline characteristics are shown in supplemental Appendix 1 on the *Blood* Web site and Table 1.

Of the 605 patients who had a pretreatment with VKA and were switched to rivaroxaban (605/1775; 34.1%), information about the main reason for switching (as indicated by the enrolling physician) was available for 514 patients (85.0%); these reasons consisted of unstable international normalized ratio (INR; 66.1%), bleeding during VKA treatment (18.9%), frequent falls (12.1%), thromboembolic events during VKA treatment (2.5%), and other (0.4%).

Rates of bleeding complications during rivaroxaban therapy

As of December 31, 2013, follow-up information was available for all 1775 rivaroxaban patients enrolled in the registry (100%). By that date, the median treatment duration with rivaroxaban was 274 days (25th and 75th percentile 126/454 days) for VTE and 388 days (25th and 75th percentile 275/543 days) for SPAF.

In the valid-for-safety analysis, the rates of major bleeding per 100 patient-years were 3.4 (95% CI 2.6-4.4) for all patients, 3.1 (95% CI 2.2-4.3) for SPAF patients, and 4.1 (95% CI 2.5-6.4) for VTE patients (Table 2). There was no statistically relevant difference between the SPAF and VTE patient groups.

Figure 1 presents the corresponding Kaplan-Meier curves for major bleeding for SPAF and VTE patients.

In the valid-for-safety analysis set, patients experiencing major bleeding during follow-up were significantly older than patients without major bleeding (79 [interquartile range (IQR) 10.5] years vs 73 [IQR 14] years; $P = .0016$) and more often had impaired renal function (22.0% vs 10.4%; $P = .0048$) (Table 1). In contrast, proportions of patients that were anticoagulation-naive (62.7% vs 60.0%; $P = .678$), with a history of stroke or systemic embolism (13.6% vs 11.4%), with coronary artery disease (23.7% vs 17.3%), or with concomitant nonsteroidal anti-inflammatory drug or antiplatelet therapy at baseline (8.5% vs 17.1%) were not significantly different between cohorts with and without major bleeding, respectively, during follow-up.

Pattern and management of bleeding complications during rivaroxaban therapy

The pattern of distribution and the management of rivaroxaban-related bleeding complications were assessed in the as-treated population (any bleeding occurring within 3 days of last intake of rivaroxaban, irrespective of the type of anticoagulation at baseline). In this analysis, 1082 bleeding events occurring in 762 patients were evaluated.

The majority of bleeding events occurred spontaneously (77.4% of all bleeding events, 71.5% of all NMCR, and 71.2% of all major bleedings, respectively; supplemental Appendix 2). In contrast, 15.7% of all bleeding events occurred after trauma (17.2% of all NMCR and 10.6% of all major bleeding events, respectively) and 6.9% occurred after surgical or interventional procedures (11.3% of all NMCR and 18.2% of all major bleeding events, respectively).

Of the 1082 bleeding events observed during rivaroxaban exposure, 637 (58.9%) were classified as ISTH minor bleeding because no physician contact or specific treatment was necessary. Another 379 events (35.0%) were classified as ISTH NMCR bleeding. These could mostly be treated conservatively and required surgical or interventional treatment in 51 cases (13.5%), mainly consisting of sutures after traumatic skin lesions, sclerotizations of mucosal bleeding, or endoscopic treatment of gastrointestinal bleeding (Table 3; supplemental Appendix 3).

Major bleeding occurred in 66 events (6.1%) and the main criterion for ISTH major bleeding was the necessity of at least 2 U RBC transfusions. Most cases of major bleeding (62.1%) could be treated conservatively, and 25 cases (37.9%) required surgical or interventional treatment, mainly endoscopic treatment of gastrointestinal bleeding.

Table 1. Patient characteristics of 1775 patients and subgroups of patients with and without major bleeding during rivaroxaban therapy

	All patients	No major bleeding	Major bleeding	*P* value: no major bleeding vs major bleeding
N (%)	1775 (100)	1716 (96.7)	59 (3.3)	
Male, n (%)	913 (51.4)	880 (51.3)	33 (55.9)	.4823
Age (y) median (IQR)	74 (14)	73 (14)	79 (10.5)	.0016
Mean BMI ± SD (kg/m$^{2)}$	28.5 ± 5.1	28.6 ± 5.1	27.6 ± 4.6	.1449
Coronary artery disease, n (%)	311 (17.5)	297 (17.3)	14 (23.7)	.2021
Prior stroke or systemic embolism, n (%)	203 (11.4)	195 (11.4)	8 (13.6)	.6023
Concomitant antiplatelet therapy or NSAID, n (%)	298 (16.8)	293 (17.1)	5 (8.5)	.0823
Impaired renal function, n (%)*	192 (10.8)	179 (10.4)	13 (22.0)	.0048
Anticoagulation-naive	1067 (60.1)	1030 (60.0)	37 (62.7)	.6784

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
*Impaired renal function was defined as current or history of GFR <50 mL/min.

Treatment with fresh frozen plasma (FFP; 0.6% of all bleeding and 9.1% of all major bleeding) or PCCs (0.6% of all bleeding and 9.1% of all major bleeding) was carried out only in patients with major bleeding events (3 patients received PCC, another 3 patients received FFP, and 3 patients received both PCC and FFP). No patient received treatment with recombinant factor VII, factor VIII inhibitor bypass activator, or antifibrinolytic agents (Table 3).

Details of the 6 cases in which PCC was given are provided in Table 4. Time between admission and PCC application ranged from 1 to 22 hours and delay in 2 patients was due to the documented last intake of rivaroxaban >24 hours before admission. All patients receiving PCC had pathologic values of coagulation parameters on admission and, in 4 cases, coagulation tests were repeated within hours of PCC administration. Only 1 case demonstrated significant improvement (INR corrected from 4.0 to 1.4; prothrombin time ratio from 17% to 62%; and activated partial thromboplastin time from 65.8 to 37.8 seconds). In the remaining 3 cases, only slight changes were seen, but last intake of rivaroxaban was >24 hours before admission in 2 of them.

Outcome of rivaroxaban-associated bleeding complications

The outcome of rivaroxaban-related bleeding complications was assessed in the as-treated population (any bleeding occurring within 3 days of last intake of rivaroxaban, irrespective of the type of anticoagulation at baseline). Outcome was established for day 30 and 90 after the onset of the index bleeding with outcome information available for all 1082 bleeding events occurring in 762 patients (100%).

Six patients (6.7%) experienced a major cardiovascular event within 90 days of a bleeding complication (in 5 cases [83.3%] after major bleeding). Detailed data for these cases are provided in supplemental Appendix 4. All cardiovascular events occurred within 35 days of the bleeding event; 4 events (66.7%) occurred within 7 days. None of the patients with cardiovascular events during follow-up was exposed to PCC during acute bleeding management.

Of the 6 patients receiving PCC therapy, 5 showed stabilization of hemorrhage during the clinical course; 4 of these survived without sequelae at day 90 postbleeding (the fifth patient died of septic pneumonia on day 16). The only PCC patient without stabilization of hemorrhage died of acute intracranial bleeding at day 7 after onset of bleeding. In this case, PCC application was delayed (5.5 hours after admission) and underdosed (18 IU/kg bodyweight; supplemental Appendix 4).

To assess mortality rates after rivaroxaban-associated bleeding, different types of bleeding were assessed. First, all-cause and bleeding-related mortality rates were assessed in the valid-for-safety set according to bleeding severity (classified by ISTH definition) using Kaplan-Meier analysis. At day 90 after rivaroxaban-associated bleeding, all-cause mortality rates were 1.2% (95% CI 0.4-2.0) for all bleeding events and 0.4% (95% CI 0.0-1.0), 1.3% (0.0-2.5), and 10.2% (2.5-17.9) for minor, NMCR or major bleeding, respectively. In contrast, bleeding-related mortality at day 90 was 5.1% (95% CI 0.0-10.7) for major bleeding.

Second, mortality was assessed for all patients in need of hospitalization for bleeding therapy in the as-treated set to allow for comparison with available VKA data. Of 98 rivaroxaban-related bleeding complications requiring hospitalization, follow-up data were available for day 30 in all cases and for day 90 in 95 cases (96.9%), given that 3 patients withdrew informed consent between day 30 and 90 postbleeding.

Death from any cause occurred in 5 patients within 30 days and in 1 additional patient before day 90 after the bleeding-related hospitalization. Therefore, case fatality rates were 5.1% for day 30 and 6.3% for day 90.

Discussion

To our knowledge, our data are the first available results regarding the pattern, management, and outcome of rivaroxaban-related bleeding complications in patients from daily care.

Rates of rivaroxaban-associated bleeding

In the valid-for-safety analysis, major bleeding rates per 100 patient-years were 3.1 (95% CI 2.2-4.3) for SPAF patients and 4.1 (95% CI 2.5-6.4) for VTE patients. Although the rate for SPAF patients was

Table 2. Bleeding rates per 100 patient-years in valid-for-safety analysis set

	All patients	SPAF	VTE	*P* value: SPAF vs VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)	
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)	.4989
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)	.4199
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)	.1585
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)	.2849

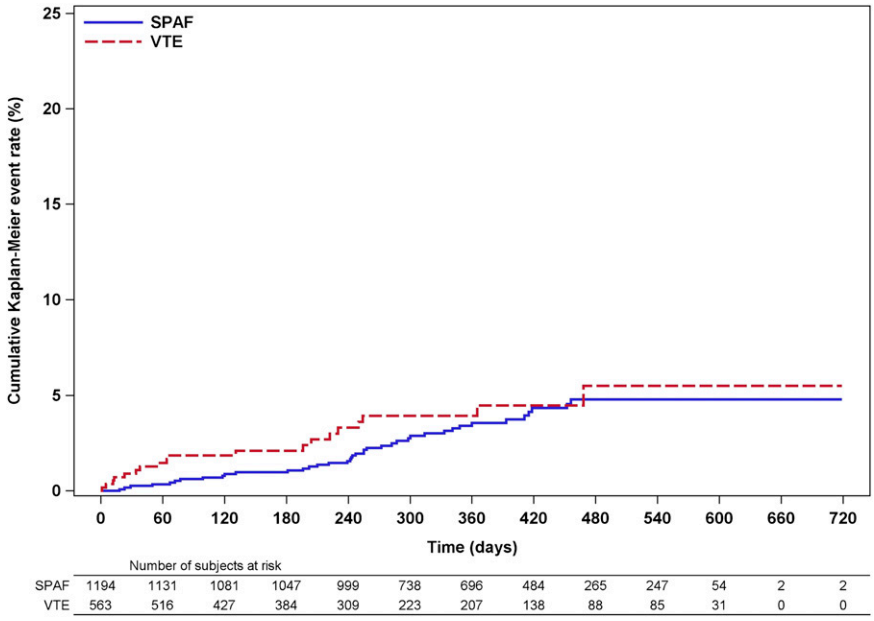

Figure 1. Kaplan-Meier estimation for first major bleeding (intention-to-treat [ITT] analysis set).

found to be in the range of the phase 3 trial data (3.4% major bleeding in Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation [ROCKET AF]), the rates for VTE patients seem much higher than those reported in the respective VTE trials (total of 1.0% major bleeding in the EINSTEIN pooled analysis). However, in the EINSTEIN trials, annualized event rates were not reported and will have exceeded 1%, given the comparatively short treatment duration of 3 to 12 months in the trials. Even more importantly, our VTE cohort was markedly older than the EINSTEIN population (68 vs 57 years), which may have contributed to the relatively high rate of major bleeding. However, the rates of major bleeding for SPAF and VTE patients were lower than those reported for VKA patients treated in daily care.[3-8] We accept that the pooling of data from SPAF and VTE patients is disputable. However, with a focus on management and outcome of bleeding events, the indication for anticoagulant treatment is less relevant, especially because our VTE cohort was on average only slightly younger than the SPAF cohort and demonstrated similar rates of cardiac or renal comorbidities or concomitant antiplatelet therapy.

Distribution pattern and management of rivaroxaban-associated bleeding

More than 90% of all rivaroxaban-associated bleeding complications were found to be nonmajor bleeding events. These rarely required any intensified treatment and "watchful waiting" was found to be effective in these situations. Only 6.1% of all bleeding events fulfilled the ISTH definition for major bleeding. However, more than 60% of these could be managed with local therapy or RBC transfusions, and only 37% of major bleeding events were treated with interventions or surgery.

Of the 1082 bleeding events (including 66 ISTH major bleeding events), PCC was given in only 6 cases. Interestingly, routine coagulation parameters such as prothrombin time or INR indicated the presence of rivaroxaban on admission in 5 of these patients and, in the remaining patient, the last intake of rivaroxaban was >24 hours before hospital admission. In contrast, activated partial thromboplastin time was less sensitive and was found to be abnormal in 3 cases only.

Furthermore, the timing of PCC application ranged between 1 and 22 hours after admission and was delayed in patients with a documented last rivaroxaban intake >24 hours before hospital admission. The dosage of PCC ranged between 18 and 47 IU/kg body weight and was adequately dosed (recommended dosage >25 IU/kg body weight[15]) in only 3 cases.

Cardiovascular events occurred in 6 patients within 90 days of the bleeding event. Interestingly, all events occurred within 35 days of bleeding and, in all cases, rivaroxaban was completely discontinued or interrupted for at least 11 days after the bleeding episode. This reflects the high impact of clinically relevant bleeding on cardiovascular risk, because bleeding complications often lead to anticoagulant treatment cessation, which has been described previously.[16-18]

None of the patients with cardiovascular events during follow-up received active pro-coagulant treatment (such as PCC) during the active bleeding situation, which is an important observation because use of PCC during bleeding management has been shown to increase the risk of cardiovascular events.[19,20]

Although it is difficult to draw meaningful conclusions from such small numbers of patients receiving PCC, the observed low incidence of PCC use is reassuring in 2 ways: first, PCC rarely seems

Table 3. Severity and management strategies of rivaroxaban-related bleeding complications in the as-treated population

1082 bleeding events in 762 patients	Conservative (no treatment/ compression/tamponade/transfusion)	Surgery or intervention	RBC	Vitamin K	FFP	PCC	rFVII
Minor 637/1082 (58.9%)	637/637 (100.0)	0	0	0	0	0	0
NMCR 379/1082 (35.0%)	328/379 (86.5)	51/379 (13.5)	0	0	0	0	0
Major 66/1082 (6.1%)	41/66 (62.1)	25/66 (37.9)	40/66 (60.6)	1/66 (1.5)	6/66 (9.1)	6/66 (9.1)	0
Total	1006/1082 (93.0)	76/1082 (7.0)	40/1082 (3.7)	1/1082 (0.1)	6/1082 (0.6)	6/1082 (0.6)	0

rFVII, recombinant factor VII; vitamin K, vitamin K supplementation.

Table 4. Detailed description of patients receiving prothrombin complex concentrate for treatment of rivaroxaban-related bleeding

Gender; age	Indication for and dosage of rivaroxaban	Site of bleeding	Time admission: PCC	PCC dosage	Coagulation state on admission	Coagulation state after PCC	Bleeding outcome assessment	Outcome at day 90
M; 80 y	SPAF; 15 mg OD ASA 100 mg (CAD with CABG, 1997; PCI, 2012)	Traumatic subdural hematoma	3.5 h	2000 IU initially, followed by 3000 IU 2 h later (47 IU/kg total)	INR 2.69 PT ratio 29% aPTT 43 s	INR 2.42 PT ratio 32% After another 3000 IU PCC: INR 2.25 PT ratio 34% aPTT 42 s	Patient also received 2 U FFP (500 mL); emergency trepanation, after 24 h: stabilization of subdural hematoma in CT scan	Pneumonia and death from septic shock at day 16
M; 82 y	SPAF with recent stroke; 20 mg OD (last intake 28 h before admission)	Intracerebral bleeding	5.5 h (delayed, since last intake of rivaroxaban >24 h; PCC only given after bleeding progression in CT scan)	2000 IU (18 IU/kg)	INR 1.33 PT ratio 63% aPTT 32.7 s	INR 1.13 PT ratio 81% aPTT 31 s	Initial progression (from 1 × 1 × 1 cm to 6 × 3 × 2 cm) of hematoma, application of PCC resulted in stabilization in follow-up CT scan, patient died of ICB	Death at day 7
M; 64 y	SPAF; 20 mg OD	Upper GI bleeding and epistaxis following acute renal failure	14 h (before GI endoscopy)	2000 IU (21 IU/kg)	INR 2.7 PT ratio 26% aPTT 49 s	Not done	Stabilization after endoscopy, transfusion, dialysis (for acute renal failure), and interruption of rivaroxaban	Survived without sequelae
F; 82 y	SPAF; 20 mg OD	Spontaneous hematothorax	1.0 h	2000 IU (39 IU/kg)	INR 1.58 PT ratio 46% aPTT 36.1 s	Not done	Patient also received 1 U FFP (250 mL) and 2 U RBC	Survived without sequelae
M; 75 y	VTE; 20 mg OD	Intraoperative bleeding during emergency cholecystectomy	22 h (delayed, since last intake of rivaroxaban >24 h; PCC only given after manifest intraoperative bleeding)	2000 IU (41 IU/kg)	INR 1.6 PT ratio 50% aPTT 31 s	INR 1.3 PT ratio 65% aPTT 35 s	Patient also received 1 U platelets, 2 g fibrinogen, 4 U FFP (1000 mL), and 2 U RBC; no further complications during or after surgery; discharge after 11 d	Survived without sequelae
F; 77 y	VTE; 15 mg OD clopidogrel 75 mg (NSTEMI, 2009)	Upper GI bleeding	1 h	1200 IU (20 IU/kg)	INR 4.0 PT ratio 17% aPTT 65.8 s	INR 1.4 PT ratio 62.1% aPTT 37.8 s	Stabilization after endoscopy	Survived without sequelae

aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CAD, coronary artery disease; CT, computed tomography; GI, gastrointestinal; ICB, intracranial bleed; IU, international units; NSTMI, non-ST segment elevation myocardial infarction; OD, once daily; PCI, percutaneous coronary intervention; PT, prothrombin time.

necessary in rivaroxaban-related bleeding and, second, treating emergency physicians are aware of the potential risks of PCC and the recommendation to use it in life-threatening situations only.[15]

On the other hand, if indicated, PCC should be given as soon as possible and the dosage should be adequately adapted according to body weight and, certainly, according to the site and severity of bleeding.

Mortality of bleeding complications during rivaroxaban therapy

Recent data from large cohorts of daily care VKA patients indicate that the case fatality rate of VKA-related major bleeding is approximately 15% to 20%[7-9] and up to 50% for intracranial bleeding,[21] despite the fact that decades of experience and specific and nonspecific reversal agents, such as vitamin K or prothrombin complex factor concentrates, are available to treat VKA-related bleeding events.[22]

The lack of experience, specific reversal agents, or coagulation tests to measure the anticoagulant activity of novel anticoagulants in emergency situations has led to considerable concern regarding the outcome of major bleeding complications during rivaroxaban therapy. On the other hand, post hoc analyses from large phase 3 trials indicate that in cases of major bleeding, both distribution pattern and outcome seem to favor NOAC treatment[10,23,24] compared with VKA-related bleeding.

Our data from a large prospective daily care cohort support these observations and clearly indicate that the outcome after rivaroxaban-related bleeding complications is acceptable, with all-cause mortality rates of 0.3% for all bleeding and 10% for major bleeding and bleeding-related mortality after major bleeding of 5.1%.

Furthermore, when bleeding leading to hospitalization was assessed, we found case fatality rates of 5.1% for day 30 and 6.3% for day 90. Caution should be used if a comparison of these findings with data from historical cohorts of VKA patients needing hospital treatment of bleeding complications is attempted. A few years ago, our group evaluated the outcome of patients with VKA-related bleeding admitted to hospitals in the administrative district of Dresden, Germany[9] (namely, the same geographical area and hospital setting as our current project). In this previous study, 290 patients hospitalized for VKA-related bleeding were enrolled over a 1-year period and case fatality rates as high as 7.6% during hospitalization and 14.1% at day 90 were found. Although direct comparisons between these 2 studies are not possible, our current data indicate that the outcome of patients hospitalized for rivaroxaban-related bleeding is at least not worse than that of patients hospitalized for VKA-related bleeding, and may even be better. In fact, a recent post hoc analysis of bleeding complications in the ROCKET AF trial demonstrated a trend toward lower all-cause mortality after major bleeding with rivaroxaban compared with warfarin (hazard ratio 0.69; 95% CI 0.46-1.04), which just failed to reach statistical significance.[24] However, future prospective studies need to perform direct comparisons to assess differences in the management and outcome of NOAC- and VKA-related bleeding complications.

Limitations

There are several limitations to our study. First of all, the design of our registry introduces the possibility of a selection bias because local physicians within the network are not instructed as to which of their patients should receive NOAC or VKA therapy. As a result, one could assume that physicians are more likely to switch patients to NOAC therapy who have VKA complications or risk factors for adverse events during VKA therapy, and, therefore, our cohort might reflect a selection of patients at high risk of cardiovascular or bleeding complications. On the other hand, one may also argue that clinicians could reserve a newly approved anticoagulant for only the healthiest of their patients, perceived to be at the lowest risk of bleeding. We cannot completely rule out either selection bias. However, demographic characteristics, comorbidities, and the large number of patients switched from VKA to NOAC because of unstable INR or bleeding events during VKA indicate that our study cohort reflects a moderate- to high-risk population. Either way, our results indicate that for our specific cohort, the overall bleeding rates are in the range of the event rates found in the respective phase 3 trials and at least are not higher than those observed in VKA patients treated in real-world settings.[7,8]

Furthermore, the evaluation of potential outcome measures relied mostly on patient contact and patient-derived information. Although all suspected outcome events were centrally adjudicated based on collected documents from family doctors and from specialists in private practices and hospitals, it is possible that some events remained unreported. However, the high rate of minor events reported in our registry and the low lost-to-follow-up rates indicate that the risk of unreported outcome events is low.

Finally, the lack of a direct comparator group (such as VKA-treated patients) could be regarded as a limitation. However, several large VKA cohort studies in daily care exist and rates, management, and outcome of VKA-related bleeding are well established,[3-9] which allows for reliable indirect comparisons. As stated previously, the design of our registry as well as the risk for selection bias during patient enrollment in the practice of the attending physicians would have limited a direct comparison with a VKA group significantly.

On the other hand, the size of our cohort of more than 1700 rivaroxaban patients and the prospective evaluation of more than 1000 rivaroxaban-related bleeding complications in unselected daily care patients is a significant strength of our study. Additionally, the use of clinically relevant end points (objectively confirmed major cardiovascular events, major bleeding complications, all-cause death) and a central adjudication process contribute to the strength and clinical impact of our data.

Conclusion

We believe that our study is the first to evaluate rates, distribution, management, and outcome of rivaroxaban-associated bleeding complications in unselected patients from daily care. Our data indicate that bleeding complications are frequent in rivaroxaban patients but mainly consist of minor or NMCR bleeding events that rarely require any treatment at all. Only approximately 6% of all bleeding events are major bleeding events, which can be managed conservatively by using tamponade, compression, or RBC transfusions in approximately 60% of events. The remaining 40% of major bleeding events required surgical or interventional treatment, but procoagulant therapy with PCC was rarely needed. Our outcome data indicate that, despite the limited clinical experience with such situations and the lack of specific antidote, the outcome of major bleeding and bleeding events leading to hospitalization in rivaroxaban patients is at least not worse than the outcome reported for major VKA bleeding in daily care patients.

Acknowledgments

The authors thank all participating physicians and hospitals who continue to be supportive in helping follow patients and provide detailed information and documentation on suspected outcome

events. The authors also thank all registry patients for their participation, support, availability, and willingness to discuss their health problems over the years, which is essential for the high data quality achieved.

The NOAC registry is supported by the Gesellschaft für Technologie und Wissenstransfer der TU-Dresden by research funds from the University Hospital Carl Gustav Carus, Dresden; the Department of Vascular Medicine; and grants from Bayer Healthcare, Boehringer Ingelheim, and Pfizer. All statistical analyses were performed by ClinStat GmbH, Institute for Clinical Research and Statistics, Köln, Germany. Final language correction was performed by Chameleon Communications International Ltd, London, UK.

Authorship

Contribution: J.B.-W. was the lead investigator and undertook the study design, central event adjudication, statistical analysis, and writing of the manuscript; K.F., F.E., V.G., C.T., U.H., and L.T. designed the study and undertook data collection and statistical analysis; S.P. undertook central event adjudication and writing of the manuscript; F.M. undertook data collection and statistical analysis; C.K. and S.W. undertook central event adjudication; K.S. was the statistician; and N.W. undertook the design of the study and writing of the manuscript.

Conflict-of-interest disclosure: J.B.-W. has received honoraria and research support from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. C.K. and S.W. have received honoraria from Bayer Healthcare. N.W. has received honoraria and research support from Bayer Healthcare, Boehringer Ingelheim, and Pfizer. The remaining authors declare no competing financial interests.

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