Original Article

Severe Hemorrhage Associated With Oral Anticoagulants

A Prospective Observational Study of the Clinical Course During Treatment With Vitamin K Antagonists or Direct Oral Anticoagulants

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Summary

Background: Few data have been published to date on outcomes after the common clinical experience of severe hemorrhage in orally anticoagulated patients.

Methods: A prospective, multicenter observational study was carried out to investigate outcomes and management in a series of consecutive patients who sustained a severe hemorrhage under treatment with vitamin K antagonists (VKA) or direct oral anti-coagulant drugs (DOAC). The primary endpoint was in-hospital death up to and including day 30 after hospital admission. The secondary endpoints were the duration of bleeding, in-hospital death due to hemorrhage (as defined by the study physician examining the patient's records), the use of antagonists, the extent of supportive measures used to stop the hemorrhage, and an assessment of causality. Consecutive patients were recruited until a predefined number of patients was reached in both groups.

Results: Among 193 patients with severe hemorrhage, 97 had been taking a VKA, and 96 had been taking a DOAC. 13.0 % (95% confidence interval [8.6; 18.5]; 25/193) of the overall group patients died in the first 30 days after hospital admission, including 17.5% ([10.6; 26.6]; 17/97) in the VKA group and 8.3% ([3.7; 15.8]; 8/96) in the DOAC group ($p = 0.085$). The median duration of bleeding was 19.8 hours in the VKA group and 27.8 hours in the DOAC group ($p = 0.632$). The in-hospital mortality due to hemorrhage was higher in the VKA group than in the DOAC group (15.5% [15/97] versus 4.2% [4/97]; $p = 0.014$). Only the use of prothrombin complex concentrates (PCCs) lowered the median duration of hemorrhage in the two patient groups. In 35% (68/193) of the patients, the hemorrhage was caused by an external influence, most commonly a fall.

Conclusion: The in-hospital mortality was higher among patients treated with VKA than among patients treated with DOAC, although the difference failed to reach statistical significance.

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Patients with nonvalvular atrial fibrillation or venous thromboembolism require anticoagulation with a vitamin K antagonists (VKA) or direct oral anti-coagulant (DOAC) in therapeutic doses (1–5). Meta-analyses of Phase III studies found that the efficacy of DOACs in preventing stroke or recurrent venous thrombosis was comparable to that of VKAs. Intracranial hemorrhage, fatal hemorrhage and clinically relevant non-severe hemorrhage occurred significantly less frequently in DOAC-treated patients compared to VKA-treated patients, while gastrointestinal hemorrhage was

more commonly observed among patients treated with rivaroxaban, edoxaban and dabigatran compared to VKA-treated patients (6, 7). Since the conduct of the pivotal studies retrospective or single-arm prospective registries on the management and outcome of severe hemorrhage have been published, showing differences in the outcomes of patients treated with DOAC versus VKA (eTable 1, 8–14).

The management of major bleeding in patients on oral anticoagulation therapy is still challenging. Prothrombin complex concentrates (PCCs) are the

antidote of choice for VKA-treated patients with severe hemorrhage. Even though specific antidotes are available, PCC is commonly used to treat severe hemorrhage in DOAC-treated patients, despite the limited evidence supporting the effectiveness of PCC in this patient population (8, 10, 11, 15–17).

There is a lack of prospective data comparing the management and outcomes in patients experiencing major bleeding during treatment with DOACs or VKAs in everyday clinical practice.

We therefore initiated the RADOA (Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamin K antagonists) registry project designed to evaluate the outcome and management of consecutive DOAC- or VKA-treated patients who were admitted to hospital with severe hemorrhages or conditions requiring urgent intervention. The registry also allows to analyze effective management strategies which can be used to control severe hemorrhage.

Methods

Study design

The RADOA registry is a prospective, observational, non-interventional, open-label, investigator-initiated multicenter German registry, documenting the management of severe hemorrhages and/or urgent interventions in patients treated with VKA or DOAC. The aims and design of this registry have already been described elsewhere (18).

The registry does not allow to calculate the prevalence rates for the various types of hemorrhage. Furthermore, comparisons between the various treatment groups (VKA vs. DOAC) are not confirmative but explorative; both noticed and unnoticed confounders may occur.

Patient recruitment continued until the predefined sample size was reached in each group. The clinical course and the outcome were prospectively documented up to and including day 30 after hospital admission. The participating centers were hospitals with interdisciplinary teams on-call 24/7 to treat anticoagulation-associated hemorrhage in their emergency departments and intensive care units. The study protocol was reviewed and approved by all relevant institutional ethics committees (IECs). An external independent monitor performed all checks (100%) of the source data on site.

Patients

Patients with major bleeding while receiving VKA or DOAC therapy were included in the registry. The modified definition of the International Society of Thrombosis and Haemostasis (ISTH) for non-surgical patients was used for hemorrhage classification (19) (definitions of major bleeding episodes in the *eBox*). The characteristics of the included patients are detailed in *Table 1*.

In 2014, the first patient was included in the registry. The majority of patients was recruited between January 2016 and March 2018.

Ethics

Since the clinical condition studied represented a medical emergency, it had to be ensured that obtaining the informed consent of the patient for inclusion in the registry did not interfere with or delay the provision of acute care. Therefore, the patients' written informed consent was only obtained after completion of acute treatment. This procedure was approved by all ethics committees. In patients who could not provide their written consent due to their poor state of health, the consent was obtained from their legal representative. Data of patients who were unconscious or died before a legal representative had been named were also included in the registry. This procedure was expressly approved by the ethics committees to prevent significant distortion of outcomes as the result of exclusion of the most severely affected patients. The study complies with the Declaration of Helsinki.

Primary and secondary endpoints

The primary endpoint was the in-hospital mortality up to and including day 30 after admission to hospital. The secondary endpoints were:

1. The time to the cessation of bleeding after hospital admission
2. The mortality associated with major bleeding
3. The use versus non-use of reversal agents with regard to the clinical outcome
4. The level of hemostasis with regard to supportive treatments
5. The efficacy of dialysis in patients treated with dabigatran, and
6. The causality of serious adverse events with regard to anticoagulants.

Hemostasis was considered achieved when the bleeding improved instantly, when the use of red blood cell transfusions, factor concentrates and/or antidotes was no longer required and/or when the local investigator documented that the bleeding had ceased completely (see definition of hemostasis in the *eBox*).

Deaths were recorded as bleeding-associated or non-bleeding-associated according to the evaluation of the local investigators. Thus, the analysis of the bleeding-associated mortality rates should be interpreted with caution.

Statistical analysis

In patients with severe hemorrhage, sample-size estimation was based on the total length of the two-sided 95% confidence intervals for the incidence of the primary endpoint. These were estimated using the PASS software (NCSS, LLC, Kaysville, Utah, USA). For a sample size of 90 patients in each group (either VKA or DOAC), the total width of the confidence interval was 13.5%, assuming an incidence of the primary endpoint of approximately 10% or less. It was 12% if an endpoint incidence below 7.5% was assumed, ensuring acceptable accuracy.

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TABLE 1

Patient characteristics at the time of inclusion in the registry (information about the DOAC daily dose and the ASA score in eTable 2)

	Total (n = 193)	VKA (n = 97)	DOAC (n = 96)	p value* ¹
Male sex	115 (59.6 %)	64 (66.0%)	51 (53.1%)	0.079
Caucasian	193 (100.0%)	97 (100.0%)	96 (100.0%)	1.000
Age (years)	79.0 (73–84)	78.0 (73–84)	80.5 (74–84)	0.482
Weight (kg)	80.0 (70–90)	80.0 (72–90)	80.0 (68–88)	0.068
Time since taking last tablet (hours)	10.8 (5.3–22.5)	15.2 (9.9–26.8)	8.3 (4.1–16.4)	0.001
Weekly VKA dose (mg)		12.8 (10.5–17.6)		
INR				
< 2		32 (33.0%)		
2–3		25 (25.8%)		
> 3		37 (38.1%)		
Indication for anticoagulation				0.081
Atrial fibrillation	150 (77.7%)	73 (75.3%)	77 (80.2%)	
Venous thrombosis	14 (7.3%)	8 (8.2%)	6 (6.2%)	
Thrombosis prophylaxis	4 (2.1%)	2 (2.1%)	2 (2.1%)	
Arterial thrombosis	3 (1.6%)	3 (3.1%)	0 (0.0%)	
Mechanical valve replacement	8 (4.1%)	7 (7.2%)	1 (1.0%)	
Other indications	9 (4.7%)	2 (2.1%)	7 (7.3%)	
Unknown	5 (2.6%)	2 (2.1%)	3 (3.1%)	
History of kidney disease	53 (27.7%)	29 (29.9%)	24 (25.0%)	0.519
CHA2DS2-VASc score	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.616
HAS-BLED score* ²	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–3.0)	0.658
Level of consciousness				0.004
Unknown	1 (0.5%)	0 (0.0%)	1 (1.0%)	–
Unconscious	32 (16.6%)	24 (24.7%)	8 (8.3%)	0.003
Arousable	21 (10.9%)	7 (7.2%)	14 (14.6%)	0.111
Awake	139 (72.0%)	66 (68.0%)	73 (76.0%)	0.262
Mechanical ventilation	34 (17.6%)	22 (22.7%)	12 (12.5%)	0.088
Hemorrhagic shock	17 (8.8%)	3 (3.1%)	14 (14.6%)	0.005
Trauma	14 (7.3%)	8 (8.2%)	6 (6.2%)	0.783
Acute renal failure	18 (9.3%)	7 (7.2%)	11 (11.5%)	0.334
Antiplatelet agents	33 (17.1%)	16 (16.5%)	17 (17.7%)	0.850
Nonsteroidal anti-inflammatory drugs	14 (7.3%)	8 (8.2%)	6 (6.2%)	0.783
Other medications with effect on hemostasis	4 (2.1%)	2 (2.1%)	2 (2.1%)	1.000

*¹Exploratory p values from two-sided tests (Fisher test, Mann-Whitney U test) for comparison of DOAC group vs. VKA group without significance correction for multiple testing; values are shown as frequency and percentages or as median and interquartile range.

*²A modified HAS-BLED score (i.e. HAS-BLED score without the item Labile INR) is used for DOAC patients, while the HAS-BLED-Score with Labile INR is used for VKA patients.

CHA2DS2-VASc score, score to determine the risk of stroke; DOAC, direct oral anticoagulants; HAS-BLED score, score to assess risk of bleeding; VKA, vitamin K antagonists

The primary statistical aim was to evaluate in-hospital mortality up to and including day 30 after hospital admission with two-sided 95% confidence intervals, using the Clopper-Pearson method. All comparisons of the primary endpoint and secondary endpoints were explorative and were not adjusted for multiple testing.

The log-rank test was used to estimate and compare the cumulative incidence curves for the primary endpoint of in-hospital mortality. As a sensitivity analysis, the odds ratio (OR) of the Fisher's exact test was compared to the odds ratio of a multivariable logistic regression analysis, taking into account indication, sex and body weight as potential confounders.

The secondary endpoint of bleeding-associated mortality was characterized by 95% confidence intervals and compared between treatment groups. In addition, competing risk models as described by Aalen-Johansen were used with a two-sided Gray test to estimate and compare cumulative incidence curves for bleeding-associated deaths and deaths due to other causes were used as competing risks.

Additional secondary exploratory analyses are shown in the *Tables 1–3*. Dichotomous and categorical variables were described by number and proportions and compared using a two-sided Fisher's exact test. Furthermore, risk differences were described using 95% score confidence intervals. Continuous and ordinal variables were described using the median (1st to 3rd quartile) and compared using two-sided Mann-Whitney U tests or Kruskal-Wallis tests. As a sensitivity analysis, a stratified Mann-Whitney U test was used to compare bleeding duration in the various patient groups according to site of bleeding (intracranial, gastrointestinal or other anatomical sites). Statistical analysis was performed using the R software, version 3.5.0 (R: Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between May 2014 and March 2018, altogether 194 consecutive patients with severe hemorrhage during oral anticoagulation therapy were included in the study at 10 sites in Germany. 97 patients received VKA (all received phenprocoumon) and 96 patients received DOACs. In the DOAC group, 41 patients on apixaban (43%), 46 patients on rivaroxaban (48%), 5 patients on edoxaban (5%), and 4 patients on dabigatran (4%) were treated. Another patient who was treated with phenprocoumon and apixaban (medication error) was excluded from further analysis.

The patients' mean age was 79 years; the demographic characteristics of the two treatment groups were comparable with regard to age, sex, indication for anticoagulation, known renal disease, and severity of the condition (*Table 1*).

On admission, intracranial hemorrhage was more frequently observed in patients treated with VKA

TABLE 2

Sites of bleeding (multiple items allowed)

Site	Total (n = 193)	VKA (n = 97)	DOAC (n = 96)	p value ^{*1}
Intracranial/intraspinal	109 (56.5 %)	64 (66.0 %)	45 (46.9 %)	0.009
Intracerebral	57 (29.5 %)	32 (33.0 %)	25 (26.0 %)	0.344
Subdural	37 (19.2 %)	23 (23.7 %)	14 (14.6 %)	0.143
Subarachnoidal	12 (6.2 %)	7 (7.2 %)	5 (5.2 %)	0.767
Epidural	1 (0.5 %)	0 (0.0 %)	1 (1.0 %)	–
Intraspinal	1 (0.5 %)	1 (1.0 %)	0 (0.0 %)	–
Unknown	1 (0.5 %)	1 (1.0 %)	0 (0.0 %)	–
Gastrointestinal tract	50 (25.9 %)	19 (19.6 %)	31 (32.3 %)	0.050
Upper	40 (20.7 %)	16 (16.5 %)	24 (25.0 %)	0.159
Lower	7 (3.6 %)	1 (1.0 %)	6 (6.2 %)	0.065
Unknown	3 (1.5 %)	2 (2.1 %)	1 (1.0 %)	1.000
Intramuscular	4 (2.1 %)	2 (2.1 %)	2 (2.1 %)	1.000
Retroperitoneal	4 (2.1 %)	2 (2.1 %)	2 (2.1 %)	1.000
Intra-articular	2 (1.0 %)	0 (0.0 %)	2 (2.1 %)	–
Intraocular	1 (0.5 %)	1 (1.0 %)	0 (0.0 %)	–
Other sites ^{*2}	23 (11.9 %)	9 (9.3 %)	14 (14.6 %)	0.275
Unknown	1 (0.5 %)	0 (0.0 %)	1 (1.0 %)	–

^{*1} Exploratory p values from two-sided tests (Fisher's exact test) for comparison of DOAC group vs. VKA group without significance correction for multiple testing; the values are shown as frequencies and percentages.

^{*2} Detailed information about other sites in *eTable 3*

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists

compared to patients receiving DOAC therapy (66.0% vs. 46.9%, $p = 0.009$) (*Table 2*), bringing about a higher rate of unconsciousness in the VKA group (24.7% vs. 8.3%, $p = 0.003$) (*Table 1*). In contrast, gastrointestinal bleeding was found less frequently in patients treated with VKA compared to patients treated with DOAC (19.6% vs. 32.3%, $p = 0.050$) (*Table 2*), resulting in a lower hemorrhagic shock rate in the VKA group (3.1% vs. 14.6%, $p = 0.005$) (*Table 1*).

Primary endpoint (in-hospital mortality)

Within the first 30 days after hospital admission, 25 of the 193 patients (13.0%, 95% confidence interval: [8.6; 18.5]) died. Of these 25 patients, 17.5% ([10.6; 26.6]; 17/97) died in the VKA group compared to 8.3% ([3.7; 15.8]; 8/96) in the DOAC group (OR = 0.43, $p = 0.085$) (*Table 3*, *Figure 1*). A sensitivity analysis found similar effects, taking into account indication, sex and body weight as potential confounders (OR = 0.40, $p = 0.069$).

Secondary endpoints

1. The cessation of bleeding occurred after a median of 19.8 hours (interquartile range: 4.9–69.9) in the

TABLE 3

Hospital mortality and causes of death within 30 days after admission

	Total ^{*1} n = 193 n (%) [95% CI]	VKA ^{*1} n = 97 n (%) [95% CI]	DOAC ^{*1} n = 96 n (%) [95% CI]	95% CI Risk difference p value ^{*2}
30-day overall in-hospital mortality	25 (13.0% [8.6; 18.5])	17 (17.5% [10.6; 26.6])	8 (8.3% [3.7; 15.8])	(-0.3%; 19.1%) 0.085
Bleeding-associated mortality	19 (9.8% [6.0; 14.9])	15 (15.5% [8.9; 24.2])	4 (4.2% [1.1; 10.3])	(3.1%; 20.4%) 0.014
Other causes of death				
Respiratory failure ^{*3}	1 (0.5% [0.0; 2.9])	1 (1.0% [0.0; 5.6])	0	(-2.9%; 5.6%) 1.000
Acute heart failure ^{*3}	2 (1.0% [0.1; 3.7])	1 (1.0% [0.0; 5.6])	1 (1.0% [0.0; 5.7])	(-4.7%; 4.7%) 1.000
Sepsis ^{*3}	2 (1.0% [0.1; 3.7])	0	2 (2.1% [0.3; 7.3])	(-7.3%; 1.8%) 0.246
Other ^{*3}	1 (0.5% [0.0; 2.9])	0	1 (1.0% [0.0; 5.7])	(-5.7%; 2.8%) 0.497

^{*1} The variables are shown as frequencies (%) with two-sided 95% confidence intervals (CI).

^{*2} p values for comparison of DOAC group vs. VKA group: two-sided Fisher test, 95% CI for risk difference as assessment interval

^{*3} Multiple selection of causes of death allowed

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists; 95% CI, 95% confidence interval

VKA group compared to 27.8 hours (7.6–63.4) in the DOAC group (p = 0.632).

2. The bleeding-related in-hospital mortality rates were higher in the VKA group compared to the DOAC group (15/97, 15.5% [8.9; 24.2] compared to 4/96, 4.2% [1.1; 10.3]; p = 0.014) (Table 3, eFigure 1). Fourteen of the 15 VKA-treated patients died as a result of intracranial hemorrhages and one patient died from retroperitoneal hemorrhage. In 40% (6/15) of the deceased VKA patients and 39.2% (31/79) of the surviving VKA patients the INR was >3.0 (p = 1.000). The median INR was comparable in both VKA groups (deceased VKA patients: INR 2.75, 1.66–3.15; surviving VKA patients: INR: 2.50, 1.65–4.00; p = 0.691). All 4 bleeding-related deaths in the DOAC group were caused by intracranial hemorrhage.

3. The majority of VKA-treated patients received PCC (72.2%, 70/97) compared to 47.9% (46/96) of patients in the DOAC group. Vitamin K was more frequently administered to the VKA-treated patients. The frequency of use of fresh frozen plasma (FFP), tranexamic acid and desmopressin was comparable in the VKA and DOAC groups (eFigure 2). The patients in the VKA group required less red blood cell concentrates compared to the patients in the DOAC group (36.1% vs. 53.1%, p = 0.021) and nominally fewer platelet concentrates (4.1% vs. 10.4%; p = 0.104) (eTables 4 and 5, eFigure 2).

4. In the VKA group, the median duration of hemorrhage was 10.0 hours among the patients treated with PCC compared to 41.5 hours among the patients without PCC treatment (p = 0.021; with stratification by bleeding site: p = 0.040) (eTable 6a). While bleed-

ing duration was found reduced in PCC-treated patients with CNS hemorrhage, no difference was found between treated and non-treated patients if the bleeding site was not located in the CNS (Figure 2a). DOAC-treated patients also showed a shorter median bleeding duration when they received PCC (11.0 hours vs. 33.1 hours among patients who had not received PCC, p = 0.009; with stratification by bleeding site: p = 0.005) (eTable 6b). All types of bleeding (CNS and non-CNS hemorrhages) showed reductions in bleeding duration after PCC treatment compared to untreated patients (Figure 2b). For all other treatments with coagulation factors or medications, no effect on bleeding duration was observed in either of the two treatment groups (eTables 7–10).

5. None of the 4 patients treated with dabigatran received hemodialysis. Two patients received idarucizumab.

6. 55 patients (28.5%; 30/97 and 25/96 of the VKA- and DOAC-treated patients, respectively) developed severe hemorrhages after falls. In 13 patients (6.7%; 5/97 and 8/96 of the VKA- and DOAC-treated patients, respectively), the bleeding was caused by other external factors (9 polytrauma, 2 suicide attempts, 1 hemorrhage after tooth extraction, 1 hemorrhage after a brawl). In the majority of patients, anticoagulation was the only identifiable factor triggering the development of major bleeding (64.8%, 125/193).

Discussion

The RADOA registry provides prospective evidence obtained in an everyday clinical setting showing that the in-hospital mortality risk is nominally higher in

VKA-treated patients with major bleeding compared to DOAC-treated patients with major bleeding, even though this difference did not reach the level of statistical significance. A comparison of the overall mortality among the two anticoagulation patient groups included in the RADOA registry with that of a recent retrospective Canadian cohort study including more than 2000 orally anticoagulated patients with major bleeding supports the robustness of the RADOA registry data. Even though the patients in the Canadian study received warfarin, while the patients in the RADOA registry were treated with phenprocoumon, the mortality rates among VKA-treated patients were comparable between the two study populations (17.5% and 15.2% in the RADOA registry and the Canadian study, respectively). Likewise, comparable mortality rates were found among DOAC-treated patients in the two studies (8.3% and 9.8% in the RADOA registry and the Canadian study, respectively) (10).

Another recently conducted prospective multicenter study with the same research topic analyzed the mortality rate within 30 days after hospital admission in 806 patients with major bleeding who received either VKA (76%) or DOAC (24%) therapies. Here again, the mortality rates among the VKA-treated patients were similar to the ones in the RADOA registry (18% vs. 17.5% in the RADOA registry) and significantly higher compared to those found for the DOAC-treated patients (9% vs. 8.3% in the RADOA registry) (20).

The second important insight from the RADOA registry was that PCC administration in DOAC-treated patients with major bleeding was associated with a 66% reduction in bleeding duration. Thanks to the RADOA registry, prospective data on the efficacy of PCC in this situation have become available for the first time.

The specific antidote for reversal of anticoagulation with factor Xa inhibitors, andexanet alpha, is not available in many hospitals. In contrast, PCC is available in a hospital setting (at least in Europe) and most clinicians are familiar with the use of PCC in patients experiencing major bleeding while receiving anticoagulation therapy. In addition, the cost of andexanet alpha may be too high for many hospitals.

We are well aware that the typical limitations of a non-randomized observational registry also apply to the RADOA registry. In everyday clinical routine, registry data can be influenced by variations in indications. In addition, it is the severity of the hemorrhage that determines whether or not an antidote is administered. Therefore, any attempt to compare different treatments could be challenged.

On the other hand, conducting randomized studies in patients with major bleeding while on oral anticoagulation is difficult and a placebo group as a comparator would be unacceptable from an ethical point of view in this life-threatening situation.

Patients were included prospectively and consecutively in this study to achieve the highest possible

FIGURE 1

Cumulative incidence curves of hospital mortality up to and including day 30 after hospital admission (two-sided log-rank test taking into account the time to death: $p = 0.053$). 17.5% (17/97) of patients died in the VKA group compared to 8.3% (8/96) in the DOAC group.

data quality and minimize bias. All included patients were overseen on site by an independent external monitor. Selection bias is minimal since all consecutive patients were included in the registry study, including patients unable to give their informed consent.

In conclusion, the RADOA registry shows that in-hospital mortality is higher in VKA-treated patients with major bleeding compared to DOAC-treated patients and that PCC may be an alternative to specific antidotes in DOAC-treated patients with major bleeding.

The results indicate that there is an urgent need for further research in this clinically relevant field. Well-designed randomized trials comparing andexanet alpha with PCC for the treatment of major hemorrhages in patients on DOAC therapy could help to improve patient care in this life-threatening situation in the future.

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FIGURE 2

The box plots show a comparison of duration of bleeding in patients treated with or without PCC.

a) VKA-treated patients; b) DOAC-treated patients (p values: Mann-Whitney U test)

DOAC, direct oral anticoagulants; PCC, prothrombin complex concentrates; VKA, vitamin K antagonists; CNS, central nervous system

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Conflict of interest

Prof. Lindhoff-Last received lecture fees and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, CSL Behring, and Aspen. She received external funds for the conduct of a clinical contract study from Bayer and Daiichi Sankyo, for a research project which she initiated from Bayer AG, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, and CSL-Behring.

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Prof. Nowak-Goettl served as a paid consultant for Bayer Vital and Boehringer Ingelheim.

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Key messages

- Data on major bleeding associated with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) are scarce.
- In this study, the outcome and management of major bleeding in patients on VKA or DOAC therapy has been analyzed prospectively.
- Overall mortality and bleeding-associated in-hospital mortality were lower in DOAC-treated patients compared to VKA-treated patients.
- The use of prothrombin complex concentrates (PCCs) was associated with shorter bleeding duration in both VKA-treated patients and DOAC-treated patients.

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Prof. Herrmann, Dr. Lindau, Dr. Lucks, Dr. Zydek, and Dr. Sümnick declare no conflict of interest.

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► Supplementary material

eFigures, eBox, eTables:
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Supplementary material to:

Severe Hemorrhage Associated With Oral Anticoagulants

A Prospective Observational Study of the Clinical Course During Treatment With Vitamin K Antagonists or Direct Oral Anticoagulants

by Edelgard Lindhoff-Last, Eva Herrmann, Simone Lindau, Stavros Konstantinides, Oliver Grottke, Ulrike Nowak-Goettl, Jessica Lucks, Barbara Zydek, Christian von Heymann, Ingvild Birschmann, Ariane Sümnick, Jan Beyer-Westendorf, Sebastian Schellong, Patrick Meybohm*, and Andreas Greinacher*

Dtsch Arztebl Int 2020; 117: 312–9. DOI: 10.3238/arztebl.2020.0312

Cumulative incidence curves of bleeding-associated in-hospital mortality up to and including day 30 after hospital admission (Gray test: $p = 0.008$)

eFIGURE 2

Comparison of treatments between the VKA and DOAC groups

a) shows box plots of the percentages of patients treated in each group (p values: Fisher's exact test).

b) shows box plots of the total doses of antidotes administered as well as the quantity of red blood cell concentrates and platelet concentrates administered within 30 days after hospital admission (p values: Mann-Whitney U test).

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists

eBOX

Methods

Definitions of major bleeding episodes

Major bleeding was defined as

- symptomatic bleeding in critical regions or organs, such as intracranial, intraspinal, gastrointestinal, intraocular, retroperitoneal, intra-articular, pericardial hemorrhages, intramuscular hemorrhages with compartment syndrome and/or
- acute life-threatening blood loss, resulting in hemodynamic instability and/or
- hemorrhages requiring acute transfusion of two or more red blood cell concentrates.

Definitions of hemostasis

In patients with intracranial hemorrhage, the cessation of bleeding was documented by follow-up CT scans which were available for 89 % (97/109) of patients. In the online case report form, only written reports of the CT scan findings were available. This information, clinical signs and symptoms at follow-up and clinical evaluations by local investigators were used to assess the cessation of intracranial hemorrhage.

In patients with gastrointestinal hemorrhage, the duration of bleeding was defined based on the stability of hemoglobin levels over time and the need for continued administration of blood transfusions.

eTABLE 1

Overview of the registries on the treatment and outcomes of bleeding in patients on oral anticoagulants

Author	Number of patients DOAC/VKA	Aim	Type of study Duration	Hemorrhage	Mortality	Conclusion	Sponsor (s)
Majeed et al. (8)	n = 84 Rivaroxaban, apixaban	Investigate the effectiveness of PCCs given for the management of MBEs in patients on rivaroxaban or apixaban	prospective, single arm cohort study, consecutive patients from 25 hospitals 2014–2016	Intracranial hemorrhage (ICH) was the most common site of bleeding requiring reversal (n = 59; 70.2%), followed by gastrointestinal bleeding in 13 (15.5%) patients. Management with PCCs was assessed as effective in 58 (69.1%) patients and ineffective in 26 (30.9%) patients.	Twenty-seven (32%) patients died within 30 days after a major bleeding event.	The administration of PCCs for the management of MBEs associated with rivaroxaban or apixaban is effective in most cases and is associated with a low risk of thromboembolism.	Octapharma
Halvorsen et al. (9)	n = 32 675 Warfarin (11 427) Dabigatran (7 925) Rivaroxaban (6 817) Apixaban (6 506)	Evaluation of bleeding outcomes in patients with AF registry to evaluate the bleeding risk of DOACs and VKA	nationwide cohort registry (using a Norwegian Patient Registry and Norwegian Prescription Registry) 2013–2016	After a median follow-up of 173 days, 2081 (6.37%) patients experienced a first major or CRNM bleeding. Use of apixaban and dabigatran were associated with a lower risk of major or clinical relevant non major bleeding compared with warfarin where as use of rivaroxaban was not. Use of dabigatran and rivaroxaban were associated with higher risk of gastrointestinal bleeding, whereas use of apixaban and dabigatran were associated with lower risk of intracranial bleeding, compared with warfarin.	not analyzed	Apixaban and dabigatran were associated with a lower risk of major or clinical relevant non major bleeding compared with warfarin. The risk of gastrointestinal bleeding was higher with rivaroxaban and dabigatran compared with warfarin	Pfizer Inc. New York

Author	Number of patients DOAC/VKA	Aim	Type of study Duration	Hemorrhage	Mortality	Conclusion	Sponsor (s)
Xu et al. (10)	n = 2 002 Warfarin (1 542) DOAC (460) (dabigatran, rivaroxaban, apixaban)	Determine and compare management strategy and outcomes in the treatment of DOAC- and warfarin-related major bleeding episodes	Retro-spective cohort- study, five hospitals across 3 cities in Ontario, comprehensive chart review 2010–2015	Intracranial hemorrhage composed a lower pro- portion of major bleeding involving DOACs com- pared with warfarin, especially subdural he- matomas. Meanwhile, a higher proportion of GI bleeding was seen in the DOAC cohort. Patients with oral anticoagulant- related major bleeding had a mean age of 81.2 years.	In-hospital mortality was lower following DOAC bleeding events (9.8% vs 15.2%; aRR, 0.66; 95% CI, 0.49–0.89), although differences in 30-day mortality did not reach statistical significance (12.6% vs 16.3%; aRR, 0.79; 95% CI, 0.61–1.03).	In patients with oral anti- coagulant-related hemor- rhage with high rates of warfarin reversal, in- hospital mortality was lower among DOAC-as- sociated bleeding events. These findings support the safety of DOACs in routine care and present useful baseline measures for evaluations of DOAC- specific reversal agents.	Canadian Institutes of Health Research, Univer- sity Hospitals Kingston Foundation, Institute for Clinical Evaluative Sciences
Albadejo et al. (11)	n = 732 Dabigatran (28%) Apixaban (7%) Rivaroxaban (64%)	Description of treatment strategies and outcomes of major bleeding events in patients on direct oral anticoagulants	Prospective single arm cohort study, 36 hospi- tals, consecutively in- cluded patients 2013–2015	Bleeding was gastroin- testinal or intracranial in 37% (212 of 732) and 24% (141 of 732) of the cases.	Mortality by day 30 was 14% (95% CI, 11 to 16). Mortality differs accord- ing to bleeding sites and was similar to previous estimates.	Management of severe bleeding is still complex, use of PCC differs on bleeding sites. Mortality differs according to bleeding sites and was similar to previous esti- mates.	Octapharma, CSL- Behring, LFB
Green et al. (12)	n = 2 192 Warfarin (81%) Dabigatran (2%) Apixaban (4%) Rivaroxaban (13%)	Describe the burden of major hemorrhage as- sociated with all available oral anticoagulants in terms of proportion of bleeds which are intra- cranial hemorrhages, in-hospital mortality and duration of hospitalization following major bleeding; (ii) identify risk factors for mortality; and (iii) com- pare the characteristics of major hemorrhage be- tween cases treated with warfarin and direct oral anticoagulants for the subgroups of patients with atrial fibrillation or venous thromboem- bolism.	Prospective cohort study from 32 UK hospitals analyzing all oral antico- agulants 2013–2016	Bleeding sites were intra- cranial (44%), gastroin- testinal (32%), and other (24%). 20% had a fatal bleed. At the time of the bleed, the majority of pa- tients were on warfarin (81%) with the remainder being on a DOAC. Two- thirds of the bleeds were reported as spontaneous and one-fifth as resulting from a fall. Bleeding was mentioned as the cause of death in 70% of cases, while in 22% it was not, and in 8% the cause of death was unknown/or referred to the coroner.	The in-hospital mortality was 21% (95% CI: 19%–23%) overall, and 33% (95% CI: 30%–36%) for patients with intra- cranial hemorrhage. The mortality rate due to major bleeding was not different between pa- tients being treated with warfarin or direct oral anticoagulants.	1 of 5 patients treated with DOACs died within 30 days. DOACs are not associated with worse outcomes compared with warfarin, despite lack of antidotes. DOAC anti- dotes and further studies are needed to investigate the impact of antidotes on patients safety.	British Society of Haematology

Author	Number of patients	Aim	Type of study	Hemorrhage	Mortality	Conclusion	Sponsor (s)
Kurogi et al. (13)	DOAC/VKA n = 2245 Warfarin, DOAC	Compare the DOAC- and warfarin-treated patients with intracranial hemorrhage based on their backgrounds, ICH severities, antiplatelet therapies at admission, hematoma removal surgeries, reversal agents, mortality rates, and modified Rankin Scale scores at discharge.	cross-sectional survey, analyzing a large nationwide Japanese discharge database 2010–2015	DOAC-associated ICHs were less likely to cause moderately or severely impaired consciousness (DOAC-associated ICHs: 31.3%, warfarin-associated ICHs: 39.4%; $p = 0.002$) or require surgical removal (DOAC-associated ICHs: 5.3%, warfarin-associated ICHs: 9.9%; $p = 0.024$) in the univariate analysis.	Propensity score analysis revealed that patients with DOAC-associated ICHs exhibited lower mortality rates within 1 day (odds ratio [OR] 4.96, $p = 0.005$), within 7 days (OR 2.29, $p = 0.037$), and during hospitalization (OR 1.96, $p = 0.039$).	DOAC-treated patients had less severe ICHs and lower mortality rates than did warfarin-treated patients, probably due to milder hemorrhages at admission and lower hematoma expansion frequencies.	Financial support by the Japanese Ministry of Health, Labor and Welfare and a KAKENHI grant from the Japan Society for the Promotion of Science
Green et al. (14)	n = 421 DOAC	1. examine the relative frequency of DOAC-related major bleeding in relation to DOAC prescriptions over the study period; 2. describe the presentation and haematological management of DOAC-related major bleeding; and 3. evaluate the association between the use of prothrombin complex concentrate (PCC) and in-hospital mortality.	prospective single arm cohort study from 32 UK hospitals 2013–2016	A total of 421 DOAC-related major bleeding episodes were reported, with 283 (67%), 89 (21%), 46 (11%) and 30 (7%) being associated with rivaroxaban, apixaban, dabigatran and edoxaban, respectively. Overall, 44% and 37% of patients presented with gastrointestinal bleeding and intracranial hemorrhage (ICH) respectively.	21.3% died in hospital within 30 days with no significant differences between the DOACs	The most frequently observed bleeding types were gastrointestinal bleedings, followed by intracranial hemorrhage. There was no evidence of benefit for PCC on in-hospital mortality.	British Society of Haematology

ARR, absolute risk reduction; DOAC, direct oral anticoagulants; ICH, intracerebral hemorrhage; PCC, prothrombin complex concentrate; VKA, vitamin K antagonists; 95% confidence intervals

eTABLE 2

Characteristics of patients on inclusion in the registry: daily doses of DOAC-treated patients. ASA score

	Total (n = 193)	VKA (n = 97)	DOAC (n = 96)	p value* [†]
Daily dose of DOAC (mg) (percentage of patients treated with the respective DOAC)				
Apixaban 5 mg			25/41 (61.0%)	
Apixaban 10 mg			13/41 (31.7%)	
Dabigatran 220 mg			1/4 (25.0%)	
Dabigatran 300 mg			2/4 (50.0%)	
Edoxaban 30 mg			2/5 (40.0%)	
Edoxaban 60 mg			2/5 (40.0%)	
Rivaroxaban 10 mg			3/46 (6.5%)	
Rivaroxaban 15 mg			13/46 (28.3%)	
Rivaroxaban 20 mg			20/46 (43.5%)	
Rivaroxaban 25 mg			2/46 (4.3%)	
Rivaroxaban 30 mg			1/46 (2.2%)	
ASA score				0.739
ASA 1	1 (0.5%)	0 (0.0%)	1 (1.0%)	
ASA 2	19 (9.8%)	9 (9.3%)	10 (10.4%)	
ASA 3	95 (49.0%)	45 (46.4%)	50 (52.1%)	
ASA 4	56 (28.9%)	29 (29.9%)	27 (28.1%)	
ASA 5	4 (2.1%)	2 (2.1%)	1 (1.0%)	

*[†] Exploratory p values from two-sided tests (Fisher test, Mann-Whitney U test) for comparison of the DOAC group with the VKA group without significance correction for multiple testing; the values are shown as frequencies and percentages.

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists

The ASA score stands for the classification of the physical status established by the American Society of Anesthesiologists (ASA):

ASA 1: A normal healthy patient

ASA 2: A patient with mild systemic disease

ASA 3: A patient with severe systemic disease which does not result in impairment

ASA 4: A patient with severe disease that is a constant threat to life

ASA 5: A dying patient who is not expected to survive the next 24 hours with or without the operation

eTABLE 3

Site of bleeding, summarized as “other bleeding sites” in Table 2

Vitamin K antagonists	
1	Ruptured abdominal aortic aneurysm
2	Retropharyngeal hemorrhage
3	Hemorrhage within sternocleidomastoid muscle, epistaxis, nasal fracture after a fall
4	Splenic rupture after a fall
5	Spontaneous pharyngeal hematoma
6	Severe hemorrhage from dialysis shunt
7	Severe epistaxis
8	Attempted suicide with phenprocoumon, diffuse generalized hematomas
9	Severe hemorrhage in the pectoral muscle after a fall
Direct oral anticoagulants	
1	Hb 5.6 g/dL, patient refused gastroscopy, bleeding site unknown
2	Hb 5.1 g/dL, bleeding site unknown
3	Menorrhagia
4	Extensive head laceration after a fall
5	Nasal fracture after a fall, epistaxis
6	Hepatic rupture after a car accident
7	Extensive head laceration after a fall
8	Hemopneumothorax after a bicycle accident
9	Hematoma of the neck and throat after a fall
10	Sternal fracture with retrosternal hemorrhage after a car accident
11	Severe epistaxis
12	Attempted suicide with apixaban and low-molecular-weight heparin; bleeding from several cuts to both thighs
13	Severe hemorrhage after a tooth extraction

Hb, hemoglobin

eTable 4A: Treatment with red blood cell transfusions in vitamin K antagonists-treated patients.

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	35 (36.1%)	12 (18.8%)	16 (84.2%)	7 (50.0%)	<0.001
Total dose (ml)	790 (500-1,247)	504 (298-632)	900 (704-2,252)	1,000 (675-1,000)	0.022
Bleeding duration (hours) in treated patients	37.5 (13.3-78.0)	20.5 (6.4-41.1)	47.5 (37.4-76.2)	13.6 (9.8-75.2)	0.367
Bleeding duration (hours) in not –treated patients,	8.5 (3.4-78.0)	9.2 (3.7-19.9)	19.8 (9.9-30.56)	5.4 (3.1-15.6)	0.369
p-value of bleeding duration treated vs. not-treated ²	0.136 ³	0.884	0.122	0.225	
Treated patients with recurrent bleedings	6/35 (17.1%)	3/12 (25.0%)	3/16 (18.8%)	0/7 (0.0%)	0.443
Not-treated patients with recurrent bleedings	4/62 (6.5%)	4/52 (7.7%)	0/3 (0.0%)	0/7 (0.0%)	1.000
p-value of recurrent bleedings treated versus not-treated ²	0.161	0.115	1.000	n.a.	
Treated patients with new thrombotic events	2/35 (5.7%)	2/12 (16.7%)	0/16 (0.0%)	0/7 (0.0%)	0.146
Not-treated patients with new thrombotic events	2/62 (3.2%)	2/52 (3.8%)	0/3 (0.0%)	0/7 (0.0%)	1.000
p-value of thrombotic events treated versus not-treated ²	0.618	0.157	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	3/35 (8.6%)	1/12 (8.3%)	0/16 (0.0%)	2/7 (28.6%)	0.077
30-day in-hospital mortality rate in not- treated patients	14/62 (22.6%)	14/52 (26.9%)	0/3 (0.0%)	0/7 (0.0%)	<0.001
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.100	0.265	n.a.	0.462	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding or other bleeding locations yield p=0.195

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 4B: Treatment with red blood cell transfusions in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	51 (53.1%)	6 (13.3%)	29 (93.5%)	16 (80.0%)	<0.001
Total dose (ml)	900 (513-1,200)	400 (262-500)	900 (600-1,200)	950 (538-1,375)	0.065
Bleeding duration (hours) in treated patients	32.0 (12.7-59.8)	30.0 (26.5-37.6)	24.1 (9.8-60.5)	51.5, (29.3-67.9)	0.340
Bleeding duration (hours) in not –treated patients,	11.0 (4.7-63.9)	11.2 (5.2-64.1)	24.5 (14.0-60.5)	4.7 (3.5-65.9)	0.771
p-value of bleeding duration treated vs. not-treated ²	0.186 ³	0.520	0.439	0.378	
Treated patients with recurrent bleedings	10/51 (19.6%)	4/6 (66.7%)	3/29 (10.3%)	3/16 (18.8%)	0.012
Not-treated patients with recurrent bleedings	4/45 (8.9%)	4/39 (10.3%)	0/2 (0.0%)	0/4 (0.0%)	1.000
p-value of recurrent bleedings treated versus not-treated ²	0.159	0.006	1.000	1.000	
Treated patients with new thrombotic events	3/51 (5.9%)	0/6 (0.0%)	1/29 (3.4%)	2/16 (12.5%)	0.513
Not-treated patients with new thrombotic events	0/45 (0.0%)	0/39 (0.0%)	0/2 (0.0%)	0/4 (0.0%)	1.000
p-value of thrombotic events treated versus not-treated ²	0.245	n.a.	1.000	1.000	
30-day in-hospital mortality rate in treated patients	4/51 (7.8%)	1/6 (16.7%)	3/29 (10.3%)	0/16 (0.0%)	0.320
30-day in-hospital mortality rate in not- treated patients	4/45 (8.9%)	4/39 (10.3%)	0/2 (0.0%)	0/4 (0.0%)	<0.001
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	0.529	1.000	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.184

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 5A: Treatment with platelet concentrates in vitamin K antagonists-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	4 (4.1%)	2 (3.1%)	1 (5.3%)	1 (7.1%)	0.420
Total dose (ml)	500 (438-625)	625 (438-812)	500.0	500.0	n.a.
Bleeding duration (hours) in treated patients	113.7	n.a.	n.a.	113.7	n.a.
Bleeding duration (hours) in not –treated patients,	13.9 (4.5-42.1)	9.6 (4.0-21.5)	42.5 (19.4-61.1)	7.6 (3.4-23.6)	0.141
p-value of bleeding duration treated vs. not-treated ²	0.269 ²	n.a.	n.a.	0.107	
Treated patients with recurrent bleedings	1/4 (25.0%)	0/2 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0.500
Not-treated patients with recurrent bleedings	9/93 (9.7%)	7/62 (11.3%)	2/18 (11.1%)	0/13 (0.0%)	0.583
p-value of recurrent bleedings treated versus not-treated ²	0.358	1.000	0.105	n.a.	
Treated patients with new thrombotic events	0/4 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1.000
Not-treated patients with new thrombotic events	4/93 (4.3%)	4/62 (6.5%)	0/18 (0.0%)	0/13 (0.0%)	0.767
p-value of thrombotic events treated versus not-treated ²	1.000	1.000	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	0/4 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	1.000
30-day in-hospital mortality rate in not- treated patients	17/93 (18.3%)	15/62 (24.2%)	0/18 (0.0%)	2/13 (15.4%)	0.779
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	1.000	n.a.	1.000	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.127

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 5b: Treatment with platelet concentrates in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	10 (10.4%)	5 (11.1%)	1 (3.2%)	4 (20.0%)	0.137
Total dose (ml)	500 (372-2,168)	500 (500-750)	330.0	1,570 (425-4,042)	0.472
Bleeding duration (hours) in treated patients	34.9 (17.5-44.1)	39.4 (39.4-44.1)	24.1	34.9 (18.8-45.2)	0.646
Bleeding duration (hours) in not –treated patients	26.1 (7.2-63.9)	20.6 (5.4-62.2)	24.3 (9.5-59.8)	51.5 (13.2-105.1)	0.387
p-value of bleeding duration treated vs. not-treated ²	0.618 ³	0.250	1.000	0.450	
Treated patients with recurrent bleedings	3/10 (30.0%)	2/5 (40.0%)	0/1 (0.0%)	1/4 (25.0%)	1.000
Not-treated patients with recurrent bleedings	11/86 (12.8%)	6/40 (15.0%)	3/30 (10.0%)	2/16 (12.5%)	0.912
p-value of recurrent bleedings treated versus not-treated ²	0.159	0.211	1.000	0.509	
Treated patients with new thrombotic events	1/10 (10.0%)	0/5 (0.0%)	0/1 (0.0%)	1/4 (25.0%)	0.500
Not-treated patients with new thrombotic events	2/86 (2.3%)	0/40 (0.0%)	1/30 (3.3%)	1/16 (6.2%)	0.283
p-value of thrombotic events treated versus not-treated ²	0.284	n.a.	1.000	0.368	
30-day in-hospital mortality rate in treated patients	4/10 (40.0%)	3/5 (60.0%)	1/1 (100.0%)	0/4 (0.0%)	0.095
30-day in-hospital mortality rate in not- treated patients	4/86 (4.7%)	2/40 (5.0%)	2/30 (6.7%)	0/16 (0.0%)	0.024
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.004	0.007	0.097	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.721

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 6a: Treatments with prothrombin complex concentrates (PCC) in vitamin K antagonist-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value ¹
PCC-treated patients	70 (72.2%)	55 (85.9%)	5 (26.3%)	10 (71.4%)	<0.001
Total dose (U)	3,000 (2000-4,200)	3,000 (2,200-4,650)	1,800 (1,500-1,800)	2,450 (2,100-3,770)	0.032
Total dose per bodyweight (U/kg)	35.7 (25.5-53.1)	40.3 (27.4-56.3)	18.8 (18.2-24.0)	34.8 (22.9-43.2)	0.078
First dose (U)	2,400 (1,800-3,000)	2,400 (2,000-3,000)	1,500 (1,200-1,800)	2,400 (1,400-2,400)	0.011
First dose per bodyweight (U/kg)	28.6 (22.8-41.4)	32.5 (24.3-45.0)	18.2 (15.0-24.0)	25.8 (16.7-32.0)	0.026
Age (years) in PCC-treated patients	78 (73.-85)	78 (73-83.5)	85 (78-86)	81 (76.5-86.5)	0.324
Age (years) in not-treated patients	78 (73-82.5)	81 (73-84)	78.5 (73.2-82.5)	76.5 (74.2-79)	0.868
p-value age treated versus not- treated ²	0.641	0.779	0.227	0.257	
ASA score in PCC-treated patients					0.578
unknown	8 (11.4%)	7 (12.7%)	1 (20.0%)	0 (0.0%)	
ASA 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ASA 2	5 (7.1%)	4 (7.3%)	1 (20.0%)	0 (0.0%)	
ASA 3	30 (42.9%)	24 (43.6%)	2 (40.0%)	4 (40.0%)	
ASA 4	26 (37.1%)	19 (34.5%)	1 (20.0%)	6 (60.0%)	
ASA 5	1 (1.4%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	
ASA score in not-treated patients					0.011
unknown	4 (14.8%)	2 (22.2%)	0 (0.0%)	2 (50.0%)	
ASA 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ASA 2	4 (14.8%)	0 (0.0%)	2 (14.3%)	2 (50.0%)	
ASA 3	15 (55.6%)	5 (55.6%)	10 (71.4%)	0 (0.0%)	
ASA 4	3 (11.1%)	1 (11.1%)	2 (14.3%)	0 (0.0%)	
ASA 5	1 (3.7%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	
p-value ASA treated versus not- treated ²	0.072	0.257	0.279	0.002	

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Bleeding duration (hours) in PCC-treated patients	10.0 (4.2-22.2)	9.1 (3.9-20.3)	59.9 (37.6-106.0)	9.9 (5.9-49.7)	0.174
Bleeding duration (hours) in not-treated patients	41.5 (16.0-62.9)	69.2 (56.4-81.2)	39.5 (17.1-51.9)	13.5 (3.0-39.9)	0.007
p-value of bleeding duration treated vs. not- treated ²	0.021 ³	0.001	0.275	0.888	
PCC-treated patients with recurrent bleedings	9/70 (12.9%)	7/55 (12.7%)	2/5 (40.0%)	0/10 (0.0%)	0.095
Not-treated patients with recurrent bleedings	1/27 (3.7%)	0/9 (0.0%)	1/14 (7.1%)	0/4 (0.0%)	1.000
p-value of recurrent bleedings treated vs. not- treated ²	0.275	0.580	0.155	n.a.	
PCC-treated patients with new thrombotic events	4/70 (5.7%)	4/55 (7.3%)	0/5 (0.0%)	0/10 (0.0%)	1.000
Not-treated patients with new thrombotic events	0/27 (0.0%)	0/9 (0.0%)	0/14 (0.0%)	0/4 (0.0%)	1.000
p-value of thrombotic events treated vs. not-treated ²	0.573	1.000	n.a.	n.a.	

PCC: 4-factor prothrombin complex concentrate

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients.

³Stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for intracranial haemorrhage, gastrointestinal bleedings, or other bleeding locations: p=0.005.

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

ASA-Score stands for the American Society of Anaesthesiologists' (ASA) classification of Physical Health:

ASA 1: patient is a completely healthy fit patient.

ASA 2: Patient has mild systemic disease.

ASA 3: Patient has severe systemic disease that is not incapacitating.

ASA 4: Patient has incapacitating disease that is a constant threat to life.

ASA 5: A moribund patient who is not expected to live 24 hour with or without surgery.

eTable 6b: Treatment with prothrombin complex concentrate (PCC) in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial haemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value ¹
PCC-treated patients	46 (47.9%)	32 (71.1%)	5 (16.1%)	9 (45.0%)	<0.001
Total dose (U)	3,000 (2, 000-4,000)	3,000 (2,475-4,050)	1,800 (1,500-2,000)	3,000 (2,400-4,200)	0.042
Total dose per bodyweight (U/kg)	40.0 (30.3-50.0)	43.5 (33.9-50.4)	31.0 (15.5-33.3)	36.8 (30.0-50.0)	0.115
First dose (U)	2,500 (1,800-3,575)	2,750 (1,800-3,600)	1,500 (1,000-1,800)	3,000 (2,400-3,600)	0.041
First dose per bodyweight (U/kg)	34.4 (24.3-46.0)	35.2 (25.5-46.7)	15.8 (13.3-31.0)	36.4 (30.0-48.0)	0.215
Age (years) in PCC-treated patients	80 (74-83)	81 (76.2-83.2)	83 (77-84)	72 (64-80)	0.093
Age (years) in not-treated patients	81 (74.2-85)	83 (79-86)	80 (74.2-85)	79 (74-84.5)	0.739
p-value age treated versus not-treated ²	0.419	0.414	0.957	0.159	
ASA score in PCC-treated patients					0.943
unknown	4 (8.7%)	3 (9.4%)	0 (0.0%)	1 (11.1%)	
ASA 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ASA 2	4 (8.7%)	2 (6.2%)	1 (20.0%)	1 (11.1%)	
ASA 3	18 (39.1%)	12 (37.5%)	2 (40.0%)	4 (44.4%)	
ASA 4	19 (41.3%)	14 (43.8%)	2 (40.0%)	3 (33.3%)	
ASA 5	1 (2.2%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	
ASA score in not-treated patients					0.069
unknown	3 (6.0%)	3 (23.1%)	0 (0.0%)	0 (0.0%)	
ASA 1	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	
ASA 2	6 (12.0%)	3 (23.1%)	2 (7.7%)	1 (9.1%)	
ASA 3	32 (64.0%)	6 (46.2%)	19 (73.1%)	7 (63.6%)	
ASA 4	8 (16.0%)	1 (7.7%)	5 (19.2%)	2 (18.2%)	
ASA 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
p-value ASA treated versus not-treated ²	0.028	0.052	0.199	0.780	

	Total (n=96)	Intracranial haemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Bleeding duration (hours) in PCC-treated patients	11.0 (4.7-48.8)	11.2 (5.1-50.4)	9.6 (7.3-18.9)	21.7 (4.2-43.2)	0.963
Bleeding duration (hours) in not –treated patients	33.1 (13.7-72.0)	36.3 (23.2-71.4)	27.5 (11.4-63.9)	53.0 (50.9-116.2)	0.135
p-value bleeding duration treated versus not-treated ²	0.009 ³	0.079	0.149	0.102	
PCC-treated patients with recurrent bleedings	9/46 (19.6%)	7/32 (21.9%)	0/5 (0.0%)	2/9 (22.2%)	0.714
Not-treated patients with recurrent bleedings	5/50 (10.0%)	1/13 (7.7%)	3/26 (11.5%)	1/11 (9.1%)	1.000
p-value recurrent bleedings treated versus not-treated ²	0.250	0.405	1.000	0.566	
PCC-treated patients with new thrombotic events	3/46 (6.5%)	0/32 (0.0%)	1/5 (20.0%)	2/9 (22.2%)	0.024
Not-treated patients with new thrombotic events	0/50 (0.0%)	0/13 (0.0%)	0/26 (0.0%)	0/11 (0.0%)	1.000
p-value thrombotic events treated versus not-treated ²	0.106	n.a.	0.161	0.189	

PCC: 4-factor prothrombin complex concentrate

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups.

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients.

³Stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for intracranial haemorrhage, gastrointestinal bleedings, or other bleeding locations: p=0.005.

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

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ASA 5: A moribund patient who is not expected to live 24 hour with or without surgery.

eTable 7A: Treatment with fresh frozen plasma in vitamin K antagonists-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	7 (7.2%)	2 (3.1%)	4 (21.1%)	1 (7.1%)	0.023
Total dose (ml)	602 (600-1,006)	551 (526-576)	930 (600-1,446)	750.0	n.a.
Bleeding duration (hours) in treated patients	29.0 (6.0-86.7)	1.3	122.8 (86.7-158.9)	7.6	n.a.
Bleeding duration (hours) in not –treated patients	14.1 (4.6-42.0)	10.0 (4.2-22.2)	39.5 (18.6-53.9)	12.3 (12.3-61.7)	0.395
p-value of bleeding duration treated vs. not-treated ²	0.895 ³	0.102	0.112	0.901	
Treated patients with recurrent bleedings	1/7 (14.3%)	0/2 (0.0%)	1/4 (25.0%)	0/1 (0.0%)	1.000
Not-treated patients with recurrent bleedings	7/90 (7.8%)	6/62 (9.7%)	1/15 (6.7%)	0/13 (0.0%)	0.569
p-value of recurrent bleedings treated versus not-treated ²	0.545	1.000	0.530	n.a.	
Treated patients with new thrombotic events	0/7 (0.0%)	0/2 (0.0%)	0/4 (0.0%)	0/1 (0.0%)	1.000
Not-treated patients with new thrombotic events	4/90 (4.4%)	4/62 (6.5%)	0/15 (0.0%)	0/13 (0.0%)	0.778
p-value of thrombotic events treated versus not- treated ²	1.000	1.000	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	0/7 (0.0%)	0/2 (0.0%)	0/4 (0.0%)	0/1 (0.0%)	1.000
30-day in-hospital mortality rate in not- treated patients	17/90 (18.9%)	15/62 (24.2%)	0/15 (0.0%)	2/13 (15.4%)	0.069
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.348	1.000	n.a.	1.000	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.745

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 7b: Treatment with fresh frozen plasma in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	9 (9.4%)	2 (4.4%)	4 (12.9%)	3 (15.0%)	0.255
Total dose (ml)	1,750 (600-4,500)	2,135 (1,942-2,328)	500 (400-600)	5,600 (5,050-7,280)	0.028
Bleeding duration (hours) in treated patients	37.1 (9.9-56.4)	49.9 (44.7-55.2)	9.8 (9.0-22.3)	45.2 (40.0-50.3)	n.a.
Bleeding duration (hours) in not –treated patients,	25.9 (6.3-64.1)	20.0 (5.5-57.3)	25.7 (11.9-61.8)	50.9 (6.6-94.1)	0.624
p-value of bleeding duration treated vs. not-treated ²	0.778 ³	0.420	0.312	0.881	
Treated patients with recurrent bleedings	3/9 (33.3%)	2/2 (100.0%)	0/4 (0.0%)	1/3 (33.3%)	0.048
Not-treated patients with recurrent bleedings	11/87 (12.6%)	6/43 (14.0%)	3/27 (11.1%)	2/17 (11.8%)	1.000
p-value of recurrent bleedings treated versus not-treated ²	0.122	0.028	1.000	0.404	
Treated patients with new thrombotic events	2/9 (22.2%)	0/2 (0.0%)	1/4 (25.0%)	1/3 (33.3%)	0.230
Not-treated patients with new thrombotic events	1/87 (1.1%)	0/43 (0.0%)	0/27 (0.0%)	1/17 (5.9%)	0.195
p-value of thrombotic events treated versus not-treated ²	0.023	n.a.	0.129	0.284	
30-day in-hospital mortality rate in treated patients	1/9 (11.1%)	1/2 (50.0%)	0/4 (0.0%)	0/3 (0.0%)	0.222
30-day in-hospital mortality rate in not- treated patients	7/87 (8.0%)	4/43 (9.3%)	3/27 (11.1%)	0/17 (0.0%)	0.109
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.559	0.212	1.000	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.823.

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 8A: Treatment with vitamin K in vitamin K antagonists-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	80 (82.5%)	57 (89.1%)	13 (68.4%)	10 (71.4%)	0.049
Total dose (ml)	40 (20-60)	40 (20-80)	20 (10-30)	35 (12-48)	0.016
Bleeding duration (hours) in treated patients	14.1 (4.8-46.0)	10.7 (3.9-23.2)	40.5 (18.3-78.0)	13.0 (7.4-52.2)	0.388
Bleeding duration (hours) in not –treated patients	11.5 (3.6-46.0)	4.6 (4.4-4.7)	44.5 (35.7-48.3)	3.1 (2.6-31.0)	0.092
p-value of bleeding duration treated vs. not-treated ²	0.392 ³	0.090	0.903	0.322	
Treated patients with recurrent bleedings	9/80 (11.2%)	7/57 (12.3%)	2/13 (15.4%)	0/10 (0.0%)	0.546
Not-treated patients with recurrent bleedings	1/17 (5.9%)	0/7 (0.0%)	1/6 (16.7%)	0/4 (0.0%)	0.588
p-value of recurrent bleedings treated versus not-treated ²	1.000	1.000	1.000	n.a.	
Treated patients with new thrombotic events	3/80 (3.8%)	3/57 (5.3%)	0/13 (0.0%)	0/10 (0.0%)	1.000
Not-treated patients with new thrombotic events	1/17 (5.9%)	1/7 (14.3%)	0/6 (0.0%)	0/4 (0.0%)	1.000
p-value of thrombotic events treated versus not-treated ²	0.544	0.378	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	13/80 (16.2%)	11/57 (19.3%)	0/13 (0.0%)	2/10 (20.0%)	0.187
30-day in-hospital mortality rate in not- treated patients	4/17 (23.5%)	4/7 (57.1%)	0/6 (0.0%)	0/4 (0.0%)	0.006
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.490	0.047	n.a.	1.000	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.357

n.a.: not available. Values are presented as frequency and percentages or median and range.

eTable 8b: Treatment with vitamin K in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	22 (22.9%)	13 (28.9%)	5 (16.1%)	4 (20.0%)	0.414
Total dose (ml)	40 (20-58)	50 (30-70)	30 (10-30)	25 (18-35)	0.102
Bleeding duration (hours) in treated patients	29.8 (8.8-48.8)	20.4 (6.9-38.5)	30.8 (28.0-38.9)	52.1 (27.3-91.1)	0.437
Bleeding duration (hours) in not –treated patients	25.7 (7.2-67.3)	21.1 (5.5-66.1)	18.9 (9.2-61.8)	45.0 (13.2-67.9)	0.711
p-value of bleeding duration treated vs. not-treated ²	0.537 ³	0.357	0.448	1.000	
Treated patients with recurrent bleedings	4/22 (18.2%)	2/13 (15.4%)	0/5 (0.0%)	2/4 (50.0%)	0.159
Not-treated patients with recurrent bleedings	10/74 (13.5%)	6/32 (18.8%)	3/26 (11.5%)	1/16 (6.2%)	0.518
p-value of recurrent bleedings treated versus not-treated ²	0.731	1.000	1.000	0.088	
Treated patients with new thrombotic events	1/22 (4.5%)	0/13 (0.0%)	0/5 (0.0%)	1/4 (25.0%)	0.182
Not-treated patients with new thrombotic events	2/74 (2.7%)	0/32 (0.0%)	1/26 (3.8%)	1/16 (6.2%)	0.319
p-value of thrombotic events treated versus not-treated ²	0.546	n.a.	1.000	0.368	
30-day in-hospital mortality rate in treated patients	4/22 (18.2%)	2/13 (15.4%)	2/5 (40.0%)	0/4 (0.0%)	0.435
30-day in-hospital mortality rate in not- treated patients	4/74 (5.4%)	3/32 (9.4%)	1/26 (3.8%)	0/16 (0.0%)	0.264
p-value of 30-day in- hospital mortality treated versus not-treated ²	0.078	0.617	0.060	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.575

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 9A: Treatment with tranexamic acid in vitamin K antagonists-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	9 (9.3%)	7 (10.9%)	1 (5.3%)	1 (7.1%)	0.874
Total dose (ml)	1,000 (1,000-2,000)	1,000 (1,000-1,000)	2,000.0	2,125.0	n.a.
Bleeding duration (hours) in treated patients	15.1 (11.5-19.8)	12.0 (11.4-18.1)	n.a.	88.8	n.a.
Bleeding duration (hours) in not –treated patients	14.1 (4.4-43.5)	9.1 (3.9-25.7)	42.5 (19.4-61.1)	7.6 (3.4-23.6)	0.169
p-value bleeding duration treated vs. not-treated ²	0.838 ³	0.988	n.a.	0.172	
Treated patients with recurrent bleedings	2/9 (22.2%)	1/7 (14.3%)	1/1 (100.0%)	0/1 (0.0%)	0.417
Not-treated patients with recurrent bleedings	8/88 (9.1%)	6/57 (10.5%)	2/18 (11.1%)	0/13 (0.0%)	0.647
p-value of recurrent bleedings treated versus not-treated ²	0.232	0.574	0.158	n.a.	
Treated patients with new thrombotic events	1/9 (11.1%)	1/7 (14.3%)	0/1 (0.0%)	0/1 (0.0%)	1.000
Not-treated patients with new thrombotic events	3/88 (3.4%)	3/57 (5.3%)	0/18 (0.0%)	0/13 (0.0%)	1.000
p-value of thrombotic events treated versus not-treated ²	0.327	0.378	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	1/9 (11.1%)	1/7 (14.3%)	0/1 (0.0%)	0/1 (0.0%)	1.000
30-day in-hospital mortality rate in not- treated patients	16/88 (18.2%)	14/57 (24.6%)	0/18 (0.0%)	2/13 (15.4%)	0.865
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	1.000	n.a.	1.000	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and untreated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.725

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 9b: Treatment with tranexamic acid in patients on direct oral anticoagulants

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	14 (14.6%)	8 (17.8%)	1 (3.2%)	5 (25.0%)	0.051
Total dose (ml)	3,000 (1250-9,750)	4,500 (1000-11,250)	3,000.0	3,000 (2,000-26,000)	0.963
Bleeding duration (hours) in treated patients	19.4 (8.5-39.1)	11.3 (7.8-24.6)	10.0	39.1 (34.9-55.2)	0.270
Bleeding duration (hours) in not-treated patients	27.5 (6.9-64.3)	26.1 (5.4-64.3)	24.9 (9.5-59.8)	51.5 (7.5-83.0)	0.803
p-value of bleeding duration treated vs. not-treated ²	0.376 ³	0.278	0.473	1.000	
Treated patients with recurrent bleedings	3/14 (21.4%)	1/8 (12.5%)	0/1 (0.0%)	2/5 (40.0%)	0.615
Not-treated patients with recurrent bleedings	11/82 (13.4%)	7/37 (18.9%)	3/30 (10.0%)	1/15 (6.7%)	0.518
p-value of recurrent bleedings treated versus not-treated ²	0.424	1.000	1.000	0.140	
Treated patients with new thrombotic events	0/14 (0.0%)	0/8 (0.0%)	0/1 (0.0%)	0/5 (0.0%)	1.000
Not-treated patients with new thrombotic events	3/82 (3.7%)	0/37 (0.0%)	1/30 (3.3%)	2/15 (13.3%)	0.041
p-value of thrombotic events treated versus not-treated ²	1.000	n.a.	1.000	1.000	
30-day in-hospital mortality rate in treated patients	1/14 (7.1%)	1/8 (12.5%)	0/1 (0.0%)	0/5 (0.0%)	1.000
30-day in-hospital mortality rate in not- treated patients	7/82 (8.5%)	4/37 (10.8%)	3/30 (10.0%)	0/15 (0.0%)	0.091
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	1.000	1.000	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

³A stratified Wilcoxon-Mann-Whitney U test for differences in bleeding duration between treated and not-treated patients stratified for CNS bleeding, gastrointestinal bleeding, or other bleeding locations: p=0.301.

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.

eTable 10a: Treatment with desmopressin in vitamin K antagonists-treated patients

	Total (n=97)	Intracranial hemorrhage (n=64)	Gastrointestinal bleedings (n=19)	Other bleedings (n=14)	p-value¹
Treated patients	1 (1.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	n.a.
Total dose (ml)	4.0	4.0	n.a.	n.a.	n.a.
Bleeding duration (hours) in treated patients	121.2	121.2	n.a.	n.a.	n.a.
Bleeding duration (hours) in not –treated patients,	13.9 (4.5-42.1)	9.3 (3.9-20.5)	42.5 (19.4-61.1)	9.9 (3.9-52.2)	0.218
p-value of bleeding duration treated vs. not-treated ²	0.233	0.313	n.a.	n.a.	
Treated patients with recurrent bleedings	0/1 (0.0%)	0/1 (0.0%)	0/0	0/0	n.a.
Not-treated patients with recurrent bleedings	10/96 (10.4%)	7/63 (11.1%)	3/19 (15.8%)	0/14 (0.0%)	0.417
p-value of recurrent bleedings treated versus not-treated ²	1.000	1.000	n.a.	n.a.	
Treated patients with new thrombotic events	0/1 (0.0%)	0/1 (0.0%)	0/0	0/0	n.a.
Not-treated patients with new thrombotic events	4/96 (4.2%)	4/63 (6.3%)	0/19 (0.0%)	0/14 (0.0%)	0.773
p-value of thrombotic events treated versus not-treated ²	1.000	1.000	n.a.	n.a.	
30-day in-hospital mortality rate in treated patients	0/1 (0.0%)	0/1 (0.0%)	0/0	0/0	n.a.
30-day in-hospital mortality rate in not- treated patients	17/96 (17.7%)	15/63 (23.8%)	0/19 (0.0%)	2/14 (14.3%)	1.000
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	1.000	n.a.	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

n.a.: not available, Values are presented as frequency and percentages or median and interquartile range.

eTable 10b: Treatment with desmopressin in patients on direct oral anticoagulants.

	Total (n=96)	Intracranial hemorrhage (n=45)	Gastrointestinal bleedings (n=31)	Other bleedings (n=20)	p-value¹
Treated patients	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	n.a.
Total dose (ml)	0.1	n.a.	n.a.	0.1	n.a.
Bleeding duration (hours) in treated patients	55.5	n.a.	n.a.	55.5	n.a.
Bleeding duration (hours) in not –treated patients	26.1 (7.2-61.1)	21.1 (5.7-59.1)	24.1 (9.6-59.1)	45.0 (7.5-83.0)	0.656
p-value of bleeding duration treated vs. not-treated ²	0.481	n.a.	n.a.	0.540	
Treated patients with recurrent bleedings	0/1 (0.0%)	0/0	0/0	0/1 (0.0%)	n.a.
Not-treated patients with recurrent bleedings	14/95 (14.7%)	8/45 (17.8%)	3/31 (9.7%)	3/19 (15.8%)	0.647
p-value of recurrent bleedings treated versus not-treated ²	1.000	n.a.	n.a.	1.000	
Treated patients with new thrombotic events	0/1 (0.0%)	0/0	0/0	0/1 (0.0%)	n.a.
Not-treated patients with new thrombotic events	3/95 (3.2%)	0/45 (0.0%)	1/31 (3.2%)	2/19 (10.5%)	0.078
p-value of thrombotic events treated versus not-treated ²	1.000	n.a.	n.a.	1.000	
30-day in-hospital mortality rate in treated patients	0/1 (0.0%)	0/0	0/0	0/1 (0.0%)	n.a.
30-day in-hospital mortality rate in not- treated patients	8/95 (8.4%)	5/45 (11.1%)	3/31 (9.7%)	0/19 (0.0%)	0.227
p-value of 30-day in- hospital mortality treated versus not-treated ²	1.000	n.a.	n.a.	n.a.	

¹Exploratory two-sided p-values (Fisher's exact test or Kruskal-Wallis test) for comparison of the three bleeding location groups

²Exploratory two-sided p-values (Fisher's exact test or Wilcoxon-Mann-Whitney U test) for comparison of treated and not-treated patients

n.a.: not available. Values are presented as frequency and percentages or median and interquartile range.