Acute subdural hematoma in patients on oral anticoagulant therapy: management and outcome

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OBJECTIVE Isolated acute subdural hematoma (aSDH) is increasing in older populations and so is the use of oral anticoagulant therapy (OAT). The dramatic increase of OAT—with direct oral anticoagulants (DOACs) as well as with conventional anticoagulants—is leading to changes in the care of patients who present with aSDH while receiving OAT. The purpose of this study was to determine the management and outcome of patients being treated with OAT at the time of aSDH presentation.

METHODS In this single-center, retrospective study, the authors analyzed 116 consecutive cases involving patients with aSDH treated from January 2007 to June 2016. The following parameters were assessed: patient characteristics, admission status, anticoagulation status, perioperative management, comorbidities, clinical course, and outcome as determined at discharge and through 6 months of follow-up. Oral anticoagulants were classified as thrombocyte inhibitors, vitamin K antagonists, and DOACs. Patients were stratified based on which type of medication they were taking, and subgroup analyses were performed. Predictors of unfavorable outcome at discharge and follow-up were identified.

RESULTS Of 116 patients, 74 (64%) had been following an OAT regimen at presentation with aSDH. The patients who were taking oral anticoagulants (OAT group) were significantly older (OR 12.5), more often comatose 24 hours postoperatively (OR 2.4), and more often had ≥ 4 comorbidities (OR 3.2) than patients who were not taking oral anticoagulants (no-OAT group). Accordingly, the rate of unfavorable outcome was significantly higher in patients in the OAT group, both at discharge (OR 2.3) and at follow-up (OR 2.2). Of the patients in the OAT group, 37.8% were taking a thrombocyte inhibitor, 54.1% a vitamin K antagonist, and 8.1% DOACs. In all cases, OAT was stopped on discovery of aSDH. For reversal of anticoagulation, patients who were taking a thrombocyte inhibitor received desmopressin 0.4 $\mu\text{g/kg}$, 1–2 g tranexamic acid, and preoperative transfusion with 2 units of platelets. Patients following other oral anticoagulant regimens received 50 IU/kg of prothrombin complex concentrates and 10 mg of vitamin K. There was no significant difference in the rebleeding rate between the OAT and no-OAT groups. The in-hospital mortality rate was significantly higher for patients who were taking a thrombocyte inhibitor (OR 3.3), whereas patients who were taking a vitamin K antagonist had a significantly higher 6-month mortality rate (OR 2.7). Patients taking DOACs showed a tendency toward unfavorable outcome, with higher mortality rates than patients on conventional OAT or patients in the vitamin K antagonist subgroup. Independent predictors for unfavorable outcome at discharge were comatose status 24 hours after surgery (OR 93.2), rebleeding (OR 9.8), respiratory disease (OR 4.1), and infection (OR 11.1) (Nagelkerke $R^2 = 0.684$). Independent predictors for unfavorable outcome at follow-up were comatose status 24 hours after surgery (OR 12.7), rebleeding (OR 3.1), age ≥ 70 years (OR 3.1), and 6 or more comorbidities (OR 3.1, Nagelkerke $R^2 = 0.466$). OAT itself was not an independent predictor for worse outcome.

CONCLUSIONS An OAT regimen at the time of presentation with aSDH is associated with increased mortality rates and unfavorable outcome at discharge and follow-up. Thrombocyte inhibitor treatment was associated with increased short-term mortality, whereas vitamin K antagonist treatment was associated with increased long-term mortality. In particular, patients on DOACs were seriously affected, showing more unfavorable outcomes at discharge as well as at follow-up. The suggested medical treatment for aSDH in both OAT and no-OAT patients seems to be effective and reasonable, with comparable rebleeding and favorable outcome rates in the 2 groups. In addition, prior OAT is not a predictor for aSDH outcome.

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KEY WORDS acute subdural hematoma; anticoagulation; direct oral anticoagulant; DOACs; outcome; management

ABBREVIATIONS aSDH = acute subdural hematoma; DOAC = direct oral anticoagulant; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICH = intracerebral hemorrhage; OAT = oral anticoagulant therapy; PCC = prothrombin complex concentrates; TF = tissue factor.

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ISOLATED acute subdural hematoma (aSDH) is a common disorder that has increased in prevalence in recent decades and is associated with substantial morbidity and mortality.^{4,18,20} Previously, multiple factors for the prognosis of aSDH have been reported. However, due to the increasing use of long-term oral anticoagulant therapy (OAT), patient OAT status at the time of aSDH presentation is becoming a more important issue.^{14,17,22,34} Indeed, in a recent case-control study of 10,010 SDH patients treated over a 15-year period, Gaist et al. found an association between the increased use of antithrombotic agents and the increased incidence of SDH.¹⁴ The outcome of aSDH in patients on OAT has been investigated in small cohorts, but no difference was detected between the OAT and non-OAT groups.^{25,30} Although most of the experimental as well as clinical studies have shown the prognostic relevance of OAT in intracranial hemorrhage, the relationship between aSDH and OAT remains unclear.^{10,13,30,35}

In patients receiving OAT who suffer intracranial hemorrhage, first-line management is the reversal of anticoagulation, and the treatment differs depending on the OAT profile. The effectiveness of desmopressin and thrombocyte concentrate in patients treated with antiplatelet agents or prothrombin complex concentrates (PCC) in patients treated with a vitamin K antagonist has been reported in several studies and has recently been addressed in 2 systematic reviews.^{6,9} Additionally, through the increasing use of direct oral anticoagulants (DOACs), intracranial hemorrhage and its management are receiving more attention. Nevertheless, there has been less study of the clinical management and outcome in patients who suffer isolated aSDH while on OAT, and to our knowledge no study exists concerning patients on DOACs.

We conducted this study to evaluate the acute management and functional outcome of patients on OAT who have isolated aSDH, a more homogeneous cohort than patients with major traumatic brain injury. By stratifying cases by anticoagulant category, our aim was to analyze the different clinical courses and outcomes associated with different types of oral anticoagulants. Furthermore, predictors for unfavorable outcome were identified to assess the influence of baseline clinical characteristics and in-hospital treatment on functional outcome, with a focus on DOACs.

Methods

Study Population and Data Collection

We conducted a retrospective study of patients with aSDH who were admitted to our hospital between January 2007 and June 2016. Acute SDH was defined radiologically as a hyperdense subdural collection. The inclusion criteria were defined as age older than 18 years and primary diagnosis of aSDH without further major signs of traumatic brain injury (in order to build a homogeneous cohort). Patients with hospital stay less than 24 hours or with combined traumatic brain injuries such as contusion, bleeding, and other intracranial hemorrhage, as well as patients who were lost to follow-up within 6 months of SDH onset, were excluded. This study was approved by the Clinical Ethics Committee of the University of Frankfurt.

Due to the short distance of our hospital from the international airport of Frankfurt, many international patients with minor or major trauma are sent to us. After acute management, these patients are typically transported back to their home countries, leading to loss of follow-up.

The following parameters were assessed: patient characteristics, anticoagulation status, admission status according to the Glasgow Coma Scale (GCS), hematoma characteristics, pre- and postoperative management, method of surgical treatment, postoperative status assessed via GCS, rebleeding, time course, and comorbidities. We defined the comorbidities as follows: hypertension, atrial fibrillation, Type 2 diabetes mellitus, cardiovascular disease, respiratory insufficiency, renal failure, hematological disease, metabolic disease, and infection (pneumonia, urinary tract infection, sepsis, and other infections).

The admission CT scan was used for radiological measurements. For volumetric calculation, the previously published ABC/2 formula was used.¹⁵ For the pre- and perioperative management, all intensive care unit and anesthesia protocols were assessed and rechecked by an independent clinician. Outcomes were determined according to the Glasgow Outcome Scale (GOS) at discharge as well as at the 6-months follow-up examination and were stratified into favorable (GOS scores of 4 and 5) and unfavorable (GOS scores 1–3) categories. The follow-up GOS scores were based on evaluations during follow-up visits to our institution when possible; for patients who did not return to the hospital for their 6-months follow-up, GOS scores were based on telephone surveys performed by 2 independent clinicians.

Medical Treatment

Patients were divided into 2 groups based on whether or not they were on OAT. Three categories of OAT were distinguished: thrombocyte inhibitor, vitamin K antagonist, and DOAC. Patients on OAT were further stratified into subgroups on the basis of OAT category, and all parameters mentioned above were compared between the OAT and no-OAT groups as well as between the OAT subgroups.

For acute management at admission, all patients on a thrombocyte inhibitor received desmopressin 4 µg/kg body weight and 1–2 g tranexamic acid; patients with a thrombocyte count of less than 100/nl were given 2 units of thrombocyte concentrate. In patients treated with phenprocoumon, the coagulation status was normalized through 50 IU/kg body weight PCC and 10 mg vitamin K replacement. Patients treated with DOACs also received 50 IU/kg body weight PCC. In this cohort, no patient had an indication for dialysis or plasmapheresis; also, idarucizumab was not available or allowed.

All patients who underwent a surgical treatment received 20 mg enoxaparin subcutaneously 10 hours after the operation, and afterward at least 40 mg enoxaparin was administered daily for thromboembolism prophylaxis. Patients who were conservatively treated received 40 mg enoxaparin regularly once a day. All other treatments were carried out according to the Brain Trauma Foundation Surgical Guidelines.⁵

Study Design

The purposes of this study were 1) to determine the acute management, clinical course, and outcome of aSDH in OAT and no-OAT patients; 2) to compare those parameters between different OAT regimens; and 3) to evaluate independent predictors for unfavorable outcome at discharge and follow-up.

Statistical Analysis

Data analysis was performed using GraphPad Prism (version 6.0, GraphPad Software Inc.) and IBM SPSS Statistics (version 22, IBM Corp.). For parametric parameters, an unpaired t-test was used. Categorical parameters were analyzed using Fisher's exact test. To assess the impact of the variables, odds ratios and 95% confidence intervals were calculated. Additionally, multivariate logistic regression analysis was conducted to obtain independent risk factors for unfavorable outcome, and Nagelkerke's R^2 was calculated. All tests were 2-sided and a p value ≤ 0.05 was considered to be statistically significant.

Results

Patient Characteristics

In total, 146 patients were identified. However, 30 foreign patients were lost to follow-up within the first 6 months and therefore excluded from the study. Therefore, 116 patients (80%) were eligible for the study. The mean age of these patients was 73 years (range 39–96 years), and 37 patients (31.9%) were female. At admission, 53 patients (45.7%) were comatose and 74 (63.8%) were following a regimen of OAT. In over 80% of patients (96 of 116 patients), craniotomy or craniectomy was performed. In 20 cases, the patients' admission status was good, without any sign of increased intracranial pressure; 7 of these patients (6% of the overall group) were treated conservatively, and 13 (11.2%) underwent a delayed bur hole procedure for hematoma evacuation, with the decision depending on the hematoma volume. Sixty patients (51.7% of the study group) were comatose 24 hours after operation, and rebleeding was observed in 27 patients (23.3%) after surgical treatment. Other parameters including comorbidities and clinical outcome are presented in detail in Table 1.

Acute Management, Clinical Course, and Outcome in Patients on OAT

Of 116 patients, 74 (63.8%) were on OAT at presentation; 28 (37.8%) of these 74 patients were on thrombocyte inhibitors, 40 (54.1%) were on vitamin K antagonists, and 6 (8.1%) were on DOACs. Patients on OAT were significantly older (77.5 ± 10.4 vs 65 ± 16.9 years, OR 12.5), were more often comatose 24 hours after operation (OR 2.3), and were more likely to have a higher total number of comorbidities (OR 3.2 for ≥ 4 comorbidities and OR 5.9 for ≥ 6). However, no statistically significant differences in OAT and no-OAT patients were observed in terms of the timing of surgery or the percentage of patients who experienced rebleeding (OAT 24.3%, no-OAT 21.4%). Among the comorbidities, hypertension (OR 6.4), atrial fibrillation (OR 7.5), diabetes mellitus Type 2 (OR 3.7), cardiovas-

cular disease (OR 7.1), and metabolic disease (OR 2.8) had statistically significant associations with unfavorable outcome. The risk of unfavorable outcome at discharge as well as at follow-up was significantly higher in the OAT group than in the no-OAT group (OR 2.3 and OR 2.2, respectively). The overall mortality rate at follow-up was 34.2%, and the mortality rate in the OAT group was almost twice as high as that in the no-OAT group (41% vs 21%, OR 2.6) (Table 1).

In the subgroup analysis, different OAT regimens were compared (Table 2). In general, patients on OAT before aSDH were older than patients who were not (Fig. 1A). However, due to the small numbers of patients on DOACs, statistical significance was not reached in this subgroup. In terms of admission status, including the presence of midline shift at admission, there was no statistically significant difference between any of the OAT regimens (Fig. 1B). Interestingly, the DOAC subgroup had the greatest midline shift (mean 11.4 mm) (Table 2). Patients in the thrombocyte inhibitor subgroup had the highest rebleeding rate (39.2%) (Fig. 2A), resulting in a significantly increased in-hospital mortality rate (OR 3.3). The DOAC subgroup had a similar in-hospital mortality rate (33.3%), although due to the small size of this group, the difference was not statistically significant (Fig. 2B). In contrast, patients in the vitamin K antagonist subgroup showed no significant increase in the in-hospital mortality rate compared with patients in the no-OAT group. Overall, there was a clear trend toward unfavorable outcome at follow-up in all OAT subgroups, correlating well with the number of comorbidities (Fig. 3A). In particular, patients in the vitamin K antagonist subgroup had a significantly increased mortality rate (42.5%) at follow-up (OR 2.7), and the highest mortality rate (50%) was observed in patients on DOACs (50%) (Fig. 3B). Additionally, patients on DOACs had a significantly lower GCS score 24 hours after surgery (OR 4.4) compared to patients in the other OAT subgroups. Comparison of the vitamin K antagonist and DOAC subgroups showed no significant difference in terms of outcome, clinical course, or number of comorbidities.

Predictors for Unfavorable Outcome at Discharge and Follow-Up

At discharge, 82 (70.7%) of 116 patients had an unfavorable outcome, and 25 patients (21.6% of the overall group) died during their hospitalization. In the univariate analysis, predictors for unfavorable outcome at discharge were preinjury OAT (OR 2.3), comatose status at admission (OR 8.2), comatose status 24 hours after operation (OR 23.6), 4 or more comorbidities (OR 5.1), and 6 or more comorbidities (OR 6.6). Among the comorbidities, respiratory disease (OR 3.3), infection (OR 4.7), and pneumonia (OR 9.1) were statistically significant parameters. In the multivariate analysis, independent predictors for unfavorable outcome at discharge were comatose status 24 hours after operation (OR 93.2), rebleeding (OR 9.8), respiratory disease (OR 4.1), and infection (OR 11.1) (Nagelkerke $R^2 = 0.684$). Interestingly, OAT was not an independent predictor for unfavorable outcome (Table 3).

Six months after aSDH, 64 (55.2%) of 116 patients had an unfavorable outcome, including 39 patients (33.6% of

TABLE 1. Comparison of characteristics of aSDH patients in the OAT and no-OAT groups

Characteristic	Total (n = 116)	OAT (n = 74)	No OAT (n = 42)	p Value	OR (95% CI)
Patient characteristics					
Age in yrs, mean	73.0 ± 12.8	77.5 ± 10.4	65 ± 16.9	0.0001	12.5 (7.5–17.5)
Female sex	37 (31.9)	26 (35.1)	11 (26.2)	NS	
Admission status					
GCS, mean	8.3 ± 4.4	8.0 ± 4.5	8.7 ± 4.3	NS	
GCS ≤6	50 (43.1)	37 (50)	16 (38.1)	NS	
Hematoma characteristics					
Vol in cm ³ , mean	100.7 ± 52.0	105.4 ± 52.2	92.5 ± 51.7	NS	
Midline shift in mm, mean	9.2 ± 6.5	9.5 ± 6.8	8.6 ± 5.9	NS	
Side					
Left	50 (43.1)	36 (48.6)	14 (33.3)	NS	
Right	58 (50)	34 (45.9)	24 (57.2)	NS	
Both	8 (6.9)	4 (5.5)	4 (9.5)	NS	
Op					
Craniotomy	66 (56.9)	47 (63.5)	19 (45.2)	0.08	2.1 (1.0–4.6)
Craniectomy	30 (25.9)	17 (23.0)	13 (31.0)	NS	
Bur hole	13 (11.2)	7 (9.5)	6 (14.3)	NS	
None*	7 (6.0)	3 (4.0)	4 (9.5)	NS	
Postop status†					
24-hr postop GCS, mean	8.0 ± 5.2	7.3 ± 5.3	9.2 ± 5.0	0.06	1.9 (0.09–3.9)
24-hr postop GCS ≤6	60 (51.7)	44 (59.5)	16 (38.1)	0.03	2.4 (1.1–5.2)
Rebleeding	27 (23.3)	18 (24.3)	9 (21.4)	NS	
Time course					
Timing of op in days, mean‡	0.8 ± 1.6	0.9 ± 2.0	0.5 ± 0.9	NS	
LOS in days, mean	9.8 ± 7.9	9.9 ± 8.1	9.5 ± 7.5	NS	
Outcome					
UF GOS at discharge	82 (70.7)	57 (77.0)	25 (59.5)	<0.05	2.3 (1.0–5.2)
Death prior to discharge	25 (21.6)	19 (25.7)	6 (14.3)	NS	
UF GOS at FU	64 (55.2)	46 (62.2)	18 (42.9)	<0.05	2.2 (1.0–4.7)
Death during FU	40 (34.5)	31 (41.9)	9 (21.4)	0.04	2.6 (1.1–6.3)
Comorbidities					
Hypertension	85 (73.3)	64 (86.5)	21 (50)	<0.0001	6.4 (2.6–15.7)
Atrial fibrillation	47 (40.5)	41 (55.4)	6 (14.3)	<0.0001	7.5 (2.8–19.8)
DM Type 2	34 (29.3)	28 (37.8)	6 (14.3)	0.01	3.7 (1.4–9.8)
CVD	74 (63.8)	59 (79.7)	15 (35.7)	<0.0001	7.1 (3.0–16.5)
Respiratory disease	45 (38.8)	27 (36.5)	18 (42.9)	NS	
Renal disease	22 (19.0)	13 (17.6)	9 (21.4)	NS	
Dementia	7 (6.0)	4 (5.4)	3 (7.1)	NS	
Metabolic disease	80 (69.0)	57 (77.0)	23 (54.8)	0.02	2.8 (1.2–6.3)
Hematologic disease	23 (19.8)	12 (16.2)	11 (26.2)	NS	
Infection	77 (66.4)	51 (68.9)	26 (61.9)	NS	
Pneumonia	49 (42.2)	33 (44.6)	16 (38.1)	NS	
UTI	12 (10.3)	9 (12.2)	3 (7.1)	NS	
Sepsis	6 (5.2)	5 (6.8)	1 (2.4)	NS	

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TABLE 1. Comparison of characteristics of aSDH patients in the OAT and no-OAT groups

Characteristic	Total (n = 116)	OAT (n = 74)	No OAT (n = 42)	p Value	OR (95% CI)
Comorbidities (<i>continued</i>)					
≥4 comorbidities	75 (64.7)	55 (74.3)	20 (47.6)	0.004	3.2 (1.4–7.1)
≥6 comorbidities	26 (22.4)	23 (31.1)	3 (7.1)	0.005	5.9 (1.6–20.9)

CVD = cardiovascular disease; DM = diabetes mellitus; FU = follow-up; LOS = length of hospital stay; NS = not statistically significant; UF = unfavorable; UTI = urinary tract infection.

Data are presented as number of patients (%) unless otherwise indicated. Mean values are presented with SDs.

* Conservative management.

† Data in this category are based on the patients who underwent surgery.

‡ Time from external/internal admission to operation.

the overall group) who did not survive. In the univariate analysis, predictors for unfavorable outcome at follow-up were same as the previous factors described above: anticoagulation (OR 2.2), comatose status at admission (OR 5.0), comatose status 24 hours after operation (OR 10.0), and ≥ 4 (OR 4.3) and ≥ 6 (OR 4.6) comorbidities. Among the comorbidities, atrial fibrillation (OR 2.5), diabetes mellitus Type 2 (OR 3.8), and respiratory disease (OR 2.2) were significant parameters. In the multivariate analysis, age 70 years or older (OR 3.1), comatose status 24 hours after operation (OR 12.7), rebleeding (OR 3.1), and ≥ 6 comorbidities (OR 4.3) were independent predictors (Nagelkerke $R^2 = 0.466$; Table 4). As in the multivariate analysis for factors related to outcome at discharge, oral anticoagulation was not an independent predictor for unfavorable outcome at the 6-month follow-up.

Discussion

In the present study we have shown that in aSDH patients, OAT at the time of presentation is associated with unfavorable outcome and a high mortality rate at discharge as well as at follow-up. Patients on thrombocyte inhibitors were prone to rebleeding, with a high mortality rate at discharge, whereas patients on vitamin K antagonists had a high mortality rate at follow-up. In particular, treatment with DOACs prior to aSDH showed no benefit with respect to hematoma volume, midline shift, or functional outcome at discharge or at follow-up. Confirmation of these findings in larger cohorts and randomized trials would be valuable.

Due to the aging population, the use of anticoagulants is increasing. In previous studies, the proportion of aSDH patients who were receiving OAT at the time of aSDH presentation was reported to be between 10% and 24%. Recent studies reported a further increase up to approximately 60%, which could be highly relevant in the future for further treatment.^{14,20,25,30} In our study patients, we observed a similarly high rate of OAT (65%) at aSDH presentation. However, to date there is a paucity of research dealing with this topic despite the high clinical relevance. Previously, Senft et al.²⁵ and Tausky et al.³⁰ analyzed a small cohort of patients with aSDH that occurred during OAT (11 and 16 patients) and showed no significant difference in functional outcome or mortality rate. In contrast, several previous studies observing anticoagulation

in intracranial hemorrhage reported anticoagulation or antiplatelet treatment at the time of presentation as an important poor prognostic marker,^{10,21,24,27,31} and one of the studies²⁰ reported a 1.7 times higher risk of mortality in patients on OAT at the time of the intracranial hemorrhage. In our study with a larger cohort of patients on OAT (n = 74), we observed similar results, with a clear significance toward unfavorable outcome and a mortality rate in the OAT group that was almost twice as high as that in the no-OAT group. However, OAT itself was not an independent predictor for unfavorable outcome at discharge or follow-up. Additionally, the similar rebleeding rate in the OAT and no-OAT groups seems to support the effectiveness of the medical treatment that was used in this case series. Independent risk factors for an unfavorable outcome at discharge were comatose status 24 hours after operation as an expression of severe traumatic brain injury, rebleeding as an additional clinical worsening factor in the acute phase, and comorbidities such as respiratory disease and infection, which are common complications in critically ill patients. Therefore, it is important to be alert to secondary complications and treat them as early as possible in the acute phase. In the chronic phase, risk factors such as older age in particular and cumulative comorbidities seem to be important predictors suggesting the need for interdisciplinary care of these patients after discharge. These results correlate well with several other studies reporting severe traumatic brain injury and comorbidities as important parameters for the further clinical course and outcome in both older and younger cohorts.^{4,32}

The acute management of OAT-related aSDH consists of the rapid reversal of anticoagulation. Regarding vitamin K antagonists, several experimental and clinical studies reported PCC as the optimal reversal treatment in a bleeding situation, more effective than any other factor substitution.^{6,13} This was well reflected in our study patients, with no significant difference observed between the vitamin K antagonist subgroup and the no-OAT group in terms of rebleeding or functional outcome. However, vitamin K antagonist treatment was associated with a higher number of comorbidities, resulting in a high mortality rate at follow-up. For patients who have been taking a thrombocyte inhibitor, there are limited treatment options for the rapid reversal of anticoagulation. Desmopressin and tranexamic acid were shown to be effective by increasing von Willebrand factor,

TABLE 2. Subgroup analysis of aSDH patients on OAT: thrombocyte inhibitor, vitamin K antagonist, and DOACs

Characteristic	No OAT (n = 42)	Th-Inhib (n = 28)	Th-Inhib vs No OAT	VKA (n = 40)	VKA vs No OAT	DOACs (n = 6)	DOACs vs No OAT	DOACs vs VKA
Patient characteristics								
Age in yrs, mean	65 ± 16.9	77.3 ± 12.4	p = 0.002; OR 12.3 (95% CI 4.9–19.7)	77.6 ± 9.1	p = 0.0001; OR 12.6 (95% CI 6.6–18.6)	77.7 ± 10.7	p = 0.08; OR 12.7 (95% CI –1.7 to 27.1)	NS
Female sex	11 (26.2)	10 (35.7)	NS	14 (35)	NS	2 (33.3)	NS	NS
Admission status								
GCS, mean	8.7 ± 4.3	8.3 ± 4.6	NS	7.7 ± 4.5	NS	8.2 ± 4.2	NS	NS
GCS ≤6	16 (38.1)	12 (42.9)	NS	22 (55)	NS	3 (50)	NS	NS
Hematoma characteristics								
Vol in cm ³ , mean	92.5 ± 51.7	100.4 ± 43.2	NS	108.9 ± 60.1	NS	105 ± 35.7	NS	NS
Midline shift in mm, mean	8.6 ± 5.9	8.4 ± 7	NS	10.1 ± 6.9	NS	11.4 ± 4.8	NS	NS
Side								
Left	14 (33.3)	15 (53.6)	NS	18 (45)	NS	3 (50)	NS	NS
Right	24 (57.2)	11 (39.2)	NS	20 (50)	NS	3 (50)	NS	NS
Both	4 (9.5)	2 (7.2)	NS	2 (5)	NS	0 (0)	NS	NS
Op								
Craniotomy	19 (45.2)	18 (64.3)	NS	24 (60)	NS	5 (83.3)	NS	NS
Craniectomy	13 (31.0)	6 (21.4)	NS	10 (25)	NS	1 (16.7)	NS	NS
Bur hole	6 (14.3)	3 (10.7)	NS	4 (10)	NS	0 (0)	NS	NS
None	4 (9.5)	1 (3.6)	NS	2 (5)	NS	0 (0)	NS	NS
Postop status								
24-hr postop GCS, mean	9.2 ± 5.0	7.9 ± 5.3	NS	7.2 ± 5.3	0.08	4.8 ± 4.5	p = 0.05; OR 4.4 (95% CI 0.1–8.7)	NS
24-hr postop GCS ≤6	16 (38.1)	15 (53.6)	NS	24 (60)	0.08	5 (83.3)	0.07	NS
Rebleeding	9 (21.4)	11 (39.2)	NS	6 (15)	NS	1 (16.7)	NS	NS
Time course								
Timing of op in days, mean	0.5 ± 0.9	0.3 ± 0.7	NS	1.1 ± 2.2	NS	2 ± 3.6	p = 0.02; OR 1.5 (95% CI 0.2–2.8)	NS
LOS in days, mean	11.1 ± 7.3	11.1 ± 8.7	NS	9.3 ± 7.6	NS	8.3 ± 8.1	NS	NS
Outcome								
UF GOS at discharge	25 (59.5)	22 (78.6)	NS	30 (75)	NS	5 (83.3)	NS	NS
F GOS at discharge	17 (40.5)	6 (21.4)	NS	10 (25)	NS	1 (16.7)	NS	NS
Death prior to discharge	6 (14.3)	10 (35.7)	p = 0.05; OR 3.3 (95% CI 1.0–10.6)	7 (17.5)	NS	2 (33.3)	NS	NS
UF GOS at FU	18 (42.9)	18 (64.3)	0.09	24 (60)	NS	4 (66.7)	NS	NS
F GOS at FU	24 (57.1)	10 (35.7)	0.09	16 (40)	NS	2 (33.3)	NS	NS
Death during FU	9 (21.4)	11 (39.2)	NS	17 (42.5)	p = 0.05; OR 2.7 (95% CI 1.0–7.1)	3 (50)	NS	NS
Comorbidities								
Hypertension	21 (50)	24 (85.7)	p = 0.005; OR 6.0 (95% CI 1.8–20.3)	35 (87.5)	p < 0.001; OR 7.0 (95% CI 2.3–21.4)	5 (83.3)	NS	NS
Atrial fibrillation	6 (14.3)	7 (25)	NS	30 (75)	p < 0.001; OR 18 (95% CI 5.9–55.3)	4 (66.7)	p = 0.01; OR 12 (95% CI 1.7–80.6)	NS
DM Type 2	6 (14.3)	11 (39.3)	p = 0.02; OR 3.9 (95% CI 1.2–12.3)	14 (35)	p = 0.04; OR 3.2 (95% CI 1.1–9.5)	3 (50)	p = 0.07; OR 6.0 (95% CI 1.0–37.0)	NS

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TABLE 2. Subgroup analysis of aSDH patients on OAT: thrombocyte inhibitor, vitamin K antagonist, and DOACs

Characteristic	No OAT (n = 42)	Th-Inhib (n = 28)	Th-Inhib vs No OAT	VKA (n = 40)	VKA vs No OAT	DOACs (n = 6)	DOACs vs No OAT	DOACs vs VKA
<i>Comorbidities (continued)</i>								
CVD	15 (35.7)	21 (75)	p = 0.002; OR 5.4 (95% CI 1.9–15.6)	33 (82.5)	p < 0.001; OR 8.5 (95% CI 3.0–23.8)	5 (83.3)	p = 0.07; OR 9 (95% CI 1.0–84.4)	NS
Respiratory disease	18 (42.9)	10 (35.7)	NS	15 (37.5)	NS	2 (33.3)	NS	NS
Renal disease	9 (21.4)	5 (17.9)	NS	7 (17.5)	NS	1 (16.7)	NS	NS
Dementia	3 (7.1)	2 (7.1)	NS	2 (5)	NS	0 (0)	NS	NS
Metabolic disease	23 (54.8)	22 (78.6)	p = 0.07; OR 3.0 (95% CI 1.0–9.0)	29 (72.5)	NS	6 (100)	p = 0.06; OR 10.8 (95% CI 1.2–99.6)	NS
Hematologic disease	11 (26.2)	6 (21.4)	NS	4 (10)	p = 0.09; OR 3.2 (95% CI 0.9–11.0)	1 (16.7)	NS	NS
Infection	26 (61.9)	20 (71.4)	NS	27 (67.5)	NS	4 (66.7)	NS	NS
Pneumonia	16 (38.1)	11 (39.3)	NS	20 (50)	NS	2 (33.3)	NS	NS
UTI	3 (7.1)	4 (14.3)	NS	4 (10)	NS	1 (16.7)	NS	NS
Sepsis	1 (2.4)	1 (3.6)	NS	3 (7.5)	NS	1 (16.7)	NS	NS
≥4 comorbidities	20 (47.6)	20 (71.4)	0.08	33 (82.5)	p = 0.001; OR 5.2 (95% CI 1.9–14.3)	5 (83.3)	NS	NS
≥6 comorbidities	3 (7.1)	7 (25)	0.08	13 (32.5)	p = 0.005; OR 6.3 (95% CI 1.6–24.1)	3 (50)	p = 0.02; OR 13 (95% CI 1.8–94.6)	NS

F = favorable; Th-Inhib = thrombocyte inhibitor; VKA = vitamin K antagonist.

Data are presented as number of patients (%) unless otherwise indicated. Mean values are presented with SDs.

factor VIII, intracellular platelet calcium/sodium ion concentration, and platelet adhesion to collagen, and by stabilizing the thrombocyte membrane. In accordance with the published guidelines, transfusion of thrombocyte concentrate is recommended in case of bleeding, but the recently published PATCH (Platelet Transfusion in Cerebral Haemorrhage) Phase III trial reported no benefit in hemorrhage

reduction and even an increased mortality rate with thrombocyte concentrate transfusion, raising crucial questions about the benefit and risk ratio of platelet transfusion.^{2,13,19} Indeed, patients on a thrombocyte inhibitor in our cohort had the most frequent rebleeding rate and a significant in-hospital mortality rate. Nonetheless, we would not recommend withholding thrombocyte concentrate transfusion.

FIG. 1. Patient age (A) and midline shift (B) in the OAT and no-OAT groups and the OAT subgroups. Th-inhibitor = thrombocyte inhibitor; vit-K antagonist = vitamin K antagonist.

FIG. 2. Rebleeding requiring reoperation (A) and mortality rates at discharge (B).

Currently, the relevance of DOACs is increasing due to their having an effect profile comparable to that of vitamin K antagonists, with a lower risk of intracerebral hemorrhage (ICH). The pathophysiological mechanisms are not fully understood, but it is postulated that the high level of tissue factor (TF) around blood vessels in the brain, which is important for the extrinsic coagulation pathway, plays an important role in the response to ICH. Because of their specific factor inhibition, DOACs do not influence the initial factor VII/VIIa interaction with TF, allowing for faster coagulation and reduced hematoma expansion.³³ Indeed, several experimental and clinical studies have reported on the benefit of DOACs in ICH.^{3,7,24,29,33} However, no such benefit was observed in patients with aSDH in our study, and prein-

jury DOAC therapy was even associated with an increased midline shift. Fleck et al. reported that the concentrations of TF depended on the location from which the tissue was obtained.¹² In particular, large amounts of TF with procoagulant activity were found in the brain, lung, and placenta.¹² This might explain why DOACs may have some benefit in intracerebral bleeding but not in extracerebral bleeding.

Medical Treatment for Reversal of DOAC Anticoagulation

Until recently, it was unclear how to prevent hematoma expansion in patients on DOACs. Some experimental animal studies have shown the reduction of hematoma expansion by applying PCC, but it was not clear whether the result could be translated to humans.^{28,36} Eerenberg et al.

FIG. 3. Unfavorable outcome (A) and mortality rates (B) at 6-month follow-up. FU = follow-up; UF = unfavorable.

TABLE 3. Predictors for unfavorable outcome at discharge

Variable	Outcome at Discharge		Univariate Analysis		Multivariate Analysis	
	UF (n = 82)	F (n = 34)	p Value	OR (95% CI)	p Value	OR (95% CI)
Patient characteristics						
Age						
Mean in yrs	4.7 ± 12.9	68.8 ± 17.1	0.06	5.6 (0.2–11.4)	NS	
≥70 yrs	58 (50)	19 (55.9)	NS			
≥80 yrs	39 (33.6)	12 (35.3)	NS			
Female sex	24 (29.3)	13 (38.2)	NS			
OAT	57 (69.5)	17 (50)	0.05	2.3 (1.0–5.2)	NS	
Admission status						
GCS, mean	6.9 ± 3.9	11.4 ± 3.8	0.0001	4.6 (2.9–6.1)	NS	
GCS ≤6	48 (58.5)	5 (14.7)	<0.0001	8.2 (2.9–23.3)	NS	
Hematoma characteristics						
Vol in cm ³ , mean	98.8 ± 48.5	105.2 ± 60.6	NS			
Midline shift in mm, mean	9.3 ± 7.0	8.9 ± 4.9	NS			
Side						
Left	34 (41.5)	16 (47.1)	NS			
Right	43 (52.4)	15 (44.1)	NS			
Both	5 (6.1)	3 (8.8)	NS			
Op						
Craniotomy	49 (59.8)	17 (50)	NS			
Craniectomy	24 (29.3)	6 (17.6)	NS			
Bur hole	4 (4.9)	3 (8.8)	NS			
None	5 (6.0)	8 (23.4)	NS			
Postop status						
24-hr postop GCS, mean	5.8 ± 4.2	13.3 ± 3.3	0.0001	7.5 (5.9–9.1)	NS	
24-hr postop GCS ≤6	57 (69.5)	3 (8.8)	<0.0001	23.6 (6.6–84.3)	<0.0001	93.2 (13.1–663.2)
Rebleeding	23 (28.0)	4 (11.8)	0.09	2.9 (0.9–9.2)	0.01	9.8 (1.6–60.7)
Time course						
Timing of op in days, mean	0.7 ± 1.8	0.7 ± 1.6	NS			
LOS in days, mean	10.3 ± 8.6	10.8 ± 5.7	NS			
Comorbidities						
Hypertension	63 (76.8)	22 (64.7)	NS			
Atrial fibrillation	38 (46.3)	9 (26.5)	0.06	2.4 (1.0–5.8)	NS	
DM Type 2	28 (34.1)	6 (17.6)	NS			
CVD	56 (68.3)	18 (52.9)	NS			
Respiratory disease	38 (46.3)	7 (20.6)	0.01	3.3 (1.3–8.5)	0.05	4.1 (1.0–16.8)
Renal disease	17 (20.7)	5 (14.7)	NS			
Dementia	6 (7.3)	1 (2.9)	NS			
Metabolic disease	61 (74.4)	19 (55.9)	0.08	2.3 (1.0–5.3)	NS	
Hematologic disease	18 (22.0)	5 (14.7)	NS			
Infection	63 (76.8)	14 (41.2)	0.0003	4.7 (2.0–11.1)	0.01	11.1 (1.8–69.9)
Pneumonia	45 (54.9)	4 (11.8)	<0.0001	9.1 (2.9–28.2)	NS	
UTI	7 (8.5)	5 (14.7)	NS			
Sepsis	5 (6.1)	1 (2.9)	NS			
≥4 comorbidities	64 (78.0)	14 (41.2)	0.0002	5.1 (2.1–12.0)		
≥6 comorbidities	24 (29.3)	2 (5.9)	0.006	6.6 (1.5–29.8)		

Data are presented as number of patients (%) unless otherwise indicated. Mean values are presented with SDs.

TABLE 4. Predictors for unfavorable outcome at follow-up

Variable	Outcome at FU		Univariate Analysis		Multivariate Analysis	
	UF (n = 64)	F (n = 52)	p Value	OR (95% CI)	p Value	OR (95% CI)
Patient characteristics						
Age						
Mean age in yrs	75.1 ± 12.7	70.3 ± 16.0	0.07	4.8 (0.5–10.1)	NS	
≥70 yrs	47 (73.4)	30 (57.7)	0.08	2.0 (0.9–4.4)	0.03	3.1 (1.1–8.8)
≥80 yrs	31 (47.4)	20 (38.5)	NS			
Female sex	20 (31.3)	17 (32.7)	NS			
OAT	46 (71.9)	28 (53.8)	0.05	2.2 (1.0–4.7)	NS	
Admission status						
GCS, mean	6.4 ± 3.7	10.4 ± 4.2	0.0001	4.0 (2.5–5.5)	NS	
GCS ≤6	40 (62.5)	13 (25)	<0.0001	5.0 (2.2–11.2)	NS	
Hematoma characteristics						
Vol in cm ³ , mean	98.8 ± 49.7	103.1 ± 55.4	NS			
Midline shift in mm, mean	9.2 ± 7.3	9.2 ± 5.3	NS			
Side						
Left	29 (45.3)	21 (40.4)	NS			
Right	31 (48.4)	27 (51.9)	NS			
Both	4 (6.3)	4 (7.7)	NS			
Op						
Craniotomy	35 (54.7)	31 (59.6)	NS			
Craniectomy	20 (31.3)	10 (19.2)	NS			
Bur hole	4 (6.3)	3 (5.8)	NS			
None	5 (7.7)	8 (15.4)	NS			
Postop status						
24-hr postop GCS, mean	5.2 ± 3.8	9.2 ± 5.3	0.0001	4.0 (2.3–5.7)	NS	
24-hr postop GCS ≤6	48 (71.9)	12 (23.1)	<0.0001	10.0 (4.2–23.6)	<0.0001	12.7 (4.6–35.0)
Rebleeding	19 (29.7)	8 (15.4)	0.08	2.3 (0.9–5.9)	0.05	3.1 (1.0–9.8)
Time course						
Timing of op in days, mean	0.6 ± 1.1	0.9 ± 2.2	NS			
LOS in days, mean	9.5 ± 8.5	11.6 ± 6.8	NS			
Comorbidities						
Hypertension	49 (76.6)	36 (69.2)	NS			
Atrial fibrillation	32 (50)	15 (28.8)	0.02	2.5 (1.1–5.4)	NS	
DM Type 2	26 (40.6)	8 (15.4)	0.004	3.8 (1.5–9.3)	NS	
CVD	44 (68.8)	30 (57.7)	NS			
Respiratory disease	30 (46.9)	15 (28.8)	0.05	2.2 (1.0–4.7)	NS	
Renal disease	15 (23.4)	7 (13.5)	NS			
Dementia	5 (7.8)	2 (3.8)	NS			
Metabolic disease	49 (76.6)	31 (59.6)	0.07	2.2 (1.0–4.9)	NS	
Hematologic disease	15 (23.4)	8 (15.4)	NS			
Infection	46 (71.9)	31 (59.6)	NS			
Pneumonia	32 (50)	17 (32.7)	0.09	2.1 (1.0–4.4)	NS	
UTI	4 (6.3)	8 (15.4)	NS			
Sepsis	4 (6.3)	2 (3.8)	NS			
≥4 comorbidities	52 (81.3)	26 (50)	0.0006	4.3 (1.9–9.9)	NS	
≥6 comorbidities	21 (32.8)	5 (9.6)	0.003	4.6 (1.6–13.2)	0.03	4.3 (1.2–15.5)

Data are presented as number of patients (%) unless otherwise indicated. Mean values are presented with SDs.

examined the effect of PCC on healthy human subjects treated with DOACs and reported that normalization of partial thromboplastin time required 24 hours.^{11,28} Despite the limited data and evidence-based studies, there is a clinical recommendation for PCC treatment in patients on DOACs. In our study, we administered PCC (50 IU/kg) to all patients on DOACs and saw no clinically significant difference in comparison to patients on a vitamin K antagonist. The result might support the recommendation of PCC treatment for patients with aSDH on DOACs.

There are promising developments in DOAC antidotes. Recently, idarucizumab, a novel antidote against dabigatran etexilate, was introduced into the market.²³ The coagulation parameters were normalized in 88%–98% of patients within minutes, and there is an ongoing Phase III trial (RE-VERSE AD) examining the effect in patients with major bleeding.²³ Additionally, Phase II trials have shown a promising effect of andexanet alfa in reversal of rivaroxaban and apixaban as well as PER977 for the reversal of edoxaban.^{1,16,26} Connolly et al.⁸ reported a positive effect of andexanet alfa in major bleeding associated with factor Xa inhibitors; they found a significant reduction of anti-Xa activity, and at 12 hours after andexanet alfa infusion 79% of patients had effective hemostasis. Hence, we have reached a turning point in DOAC reversal treatment, and the future is promising. Nonetheless, not every hospital will have the antidotes available, especially in emerging countries. Therefore, treatment with PCC (50 IU/kg body weight) seems to be a reasonable alternative, if DOAC antidotes are not available.

Limitations and Generalizability

Some limitations of this study should be considered. First, the number of patients who were on DOACs ($n = 6$) is small. A larger number of patients will have to be evaluated to reinforce the results of this analysis. Second, 30 foreign patients had to be excluded due to loss of follow-up. Still, the OAT rate in this cohort was 70%, with an associated unfavorable outcome rate of 77% at discharge, which is comparable with the main result. Therefore, the loss of these 30 patients might not greatly influence the main message of this study. Third, for dabigatran etexilate, an antidote (idarucizumab) is available, and we expect at least 2 antidotes for other DOACs to become available in the next 12–24 months (andexanet alfa and ciraparantag).

Nonetheless, additional data on DOACs and aSDH are still needed. Patients in different clinics may be treated differently, and additional analyses and comparisons of different treatment options are needed. Moreover, even after antidotes are developed and approved for clinical use, they will be expensive and may not be available in all cases and settings where they might be needed. Thus it remains important to consider other means of optimizing coagulation status in patients who experience aSDH while taking DOACs.

Conclusions

In our series of 116 cases of aSDH, 63% of the patients were taking anticoagulant medication before SDH, and patients on OAT had unfavorable outcome at discharge as

well as at follow-up despite successfully achieved hemostasis. Indeed, the negative prognostic factor was not OAT itself, but rather the cumulative comorbidity burden. Patients on a thrombocyte inhibitor had a higher rebleeding and mortality rate at discharge, whereas patients on a vitamin K antagonist were mainly affected at follow-up. Patients on DOACs were prone to unfavorable outcome and high mortality at discharge as well as at follow-up. However, in comparison with patients treated with a vitamin K antagonist, there was no difference in terms of outcome. Therefore, for patients on DOACs, treatment with PCC (50 IU/kg body weight) seems to be an effective alternative, if antidotes are not available. In the future, it might be interesting to evaluate the newly developed DOAC antidotes in patients with aSDH to determine whether these antidotes can improve the clinical course and functional outcome of this devastating condition.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Won, Dubinski, Cattani, Konzalla. Acquisition of data: Won, Dubinski. Analysis and interpretation of data: Won, Konzalla. Drafting the article: Won, Dubinski. Critically revising the article: Won, Cattani, Seifert, Konzalla. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Won. Statistical analysis: Won, Bruder, Konzalla. Administrative/technical/material support: Bruder, Cattani, Seifert, Konzalla. Study supervision: Seifert, Konzalla.

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