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Letter to the Editors-in-Chief

Long-term mortality after DOAC-associated intracranial haemorrhage

Dear Editors,

Intracranial haemorrhage on antithrombotic treatment is a potentially life-threatening disease with high rates of morbidity and mortality. After introduction of direct oral anticoagulants (DOAC) for the prevention and treatment of thromboembolic diseases, concerns were raised that bleeding complications such as intracranial haemorrhage could exacerbate in light of unavailable specific antidotes. However, in recent years it has been well-established that intracranial haemorrhage occurs less frequently in patients treated with DOAC compared to patients treated with vitamin K antagonists (VKA) [1]. Moreover, there is a growing body of evidence that patients who do develop intracranial haemorrhage during DOAC treatment have comparable or even more favourable short-term mortality rates compared to patients with VKA-associated intracranial haemorrhage [2]. The long-term mortality of patients with DOAC-associated intracranial haemorrhage is currently unknown as this issue has not yet been investigated.

In 2015, we reported our initial experiences with patients treated for DOAC-associated intracranial haemorrhage at our institution in *Thrombosis Research* [3]. A total of 55 patients were analysed and their 30-day mortality rate of 20% was consistent with data reported for patients with VKA-associated intracranial haemorrhage. In order to analyse the three-year mortality rate in these patients, we contacted local authorities to gain information on their survival status. In Germany, the death of a person has to be reported to local authorities by law within three days. Patient characteristics have been described in detail previously [3] and the main findings are described in Table 1. Data on history of trauma within 24 h prior to admission were analysed and patients were classified into two categories (traumatic intracranial haemorrhage and non-traumatic intracranial haemorrhage). For statistical comparison between both groups, the p values for categorial variables were derived from the Fisher's exact test and the student's two-sided *t*-test was used for the comparison of continuous variables. We used the Wilcoxon rank sum test for comparison of Glasgow coma scale (GCS) scores between both groups and the Gehan-Breslow-Wilcoxon test for comparison of survival curves. A p value of < 0.05 was considered statistically significant. All tests were performed with GraphPad Prism 8 (GraphPad Software, La Jolla, USA).

The overall three-year mortality rate was 47% and no significant difference was observed between patients with traumatic and non-traumatic intracranial haemorrhage (55% vs. 38%; $p = 0.282$) (Table 1). However, analysis of Kaplan-Meier survival curves demonstrated a higher survival in patients with non-traumatic intracranial haemorrhage compared to traumatic intracranial haemorrhage ($p = 0.041$) (Fig. 1). Patients with traumatic intracranial haemorrhage had significantly lower platelet levels on admission than patients with non-traumatic intracranial haemorrhage (202 vs. 242 $10^3/\mu L$; $p = 0.035$) and suffered more frequently of diabetes mellitus (41% vs. 12%; $p = 0.017$). These patients also had a higher rate of subarachnoid haemorrhage in computed tomography scans (41% vs. 4%; $p = 0.001$) and a higher proportion underwent medical treatment alone without neurosurgical intervention (59% vs. 4%; $p < 0.0001$).

Patients with spontaneous intracerebral haemorrhage have a poor prognosis, regardless of anticoagulation treatment. Zia and colleagues analysed a cohort of 474 patients with spontaneous intracerebral haemorrhage and found a three-year mortality rate of 49% [4]. In their study, oral anticoagulation treatment in 44 patients did not increase the risk of death at three years. A meta-analysis of 122 studies revealed a five-year mortality rate of 70.8% in patients with spontaneous intracerebral haemorrhage [5]. Patients who require anticoagulation therapy are particularly prone to thromboembolic events and their underlying medical conditions have a crucial impact on survival following intracranial haemorrhage. During in-hospital treatment of patients, thromboprophylaxis was carried out using elastic stockings and administration of enoxaparin (Clexane®, Sanofi-Aventis, Frankfurt, Germany). On hospital discharge or transferral, we recommended re-assessment of the indication for anticoagulation therapy not earlier than three weeks after bleeding event and after repeated CT imaging. Unfortunately, we have no information on re-initiation of antithrombotic treatment, rates of thromboembolism and recurrent intracranial haemorrhage in patients. This topic is of utmost importance and requires further investigation. Several studies have suggested that re-initiation of anticoagulation therapy following intracranial haemorrhage significantly reduces ischemic stroke and thromboembolism while it does not increase the risk of recurrent intracranial haemorrhage [6].

The mortality rate of 47%, three years after hospital admission, in the present study is consistent with reported data on intracranial haemorrhage survival rates in the literature. This finding may indicate that DOAC-associated intracranial haemorrhage is not associated with worse long-term mortality compared to intracranial haemorrhage without anticoagulation therapy. However, a major limitation of our study is the lack of data on the neurological outcome of patients. Assessment scores such as the modified Rankin Scale (mRS) or Glasgow Outcome Scale (GOS-E) are more suitable parameters to evaluate the outcome of patients following acute brain injury. Furthermore, it has to be considered that all types of intracranial haemorrhage were included in our study as inclusion was not limited to spontaneous intracerebral haemorrhage. Patients with chronic subdural haemorrhage were also included in this analysis and this subtype of intracranial haemorrhage is associated with more favourable patient outcomes. Manickam and colleagues reported a 5-year mortality rate of 35% in patients treated for chronic subdural haematoma [7]. In their study, warfarin use prior to hospital admission was associated with decreased long-term survival.

Importantly, substantial pathophysiological differences between traumatic and non-traumatic intracranial haemorrhage have to be considered. Although intracranial haemorrhage was considered 'traumatic' in patients with reported trauma within 24 h prior to hospital

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Table 1
Characteristics of patients with intracranial haemorrhage during DOAC-treatment.

Characteristic	All patients	Traumatic	Non-traumatic	p-Value
No. of patients	55	29	26	/
Gender				
Male	34 (62%)	19 (66%)	15 (58%)	0.589
Female	21 (38%)	10 (34%)	11 (44%)	
Mean age	75 ± 11	75 ± 14	76 ± 8	0.717
Anticoagulation therapy				
Apixaban	7 (13%)	3 (10%)	4 (15%)	0.696
Dabigatran	6 (11%)	2 (7%)	4 (15%)	0.406
Rivaroxaban	42 (76%)	24 (83%)	18 (69%)	0.343
Reason for anticoagulation				
Atrial fibrillation	46 (84%)	22 (76%)	24 (92%)	0.149
Thrombosis	5 (9%)	5 (17%)	0 (0%)	0.053
Pulmonary embolism	3 (5%)	2 (7%)	1 (4%)	1.000
Unclear	1 (2%)	0 (0%)	1 (4%)	0.473
Laboratory values				
INR	1.15 ± 0.16	1.18 ± 0.18	1.12 ± 0.14	0.154
aPTT (s)	28.9 ± 5.7	30.0 ± 5.0	27.8 ± 6.2	0.160
Platelet count ($\times 10^3$/μL)	220 ± 68	202 ± 61	242 ± 70	0.035
GFR (ml/min)	74.8 ± 21.0	69.6 ± 24.6	80.3 ± 14.8	0.065
Anti Xa assay rivaroxaban (ng/ml)	124 ± 97	176 ± 120	91 ± 67	0.068
Intracranial pathology				
Subdural haemorrhage	24 (44%)	11 (38%)	13 (50%)	0.422
Intracerebral haemorrhage	18 (33%)	8 (28%)	10 (38%)	0.566
Subarachnoid haemorrhage	13 (24%)	12 (41%)	1 (4%)	0.001
Clinical presentation				
Median GCS (IQR)	14 (11–15)	14 (14–15)	14 (9–15)	0.143[a]
GCS 13–15	40 (73%)	24 (83%)	16 (62%)	0.129
GCS 9–12	5 (9%)	1 (3%)	4 (15%)	0.178
GCS < 9	10 (18%)	4 (14%)	6 (23%)	0.490
Comorbidities				
Arterial hypertension	44 (80%)	21 (72%)	23 (88%)	0.185
Coronary heart disease	16 (29%)	11 (40%)	5 (19%)	0.149
Diabetes mellitus	15 (27%)	12 (41%)	3 (12%)	0.017
Cancer disease	3 (5%)	1 (3%)	2 (8%)	0.598
Antiplatelet therapy	7 (13%)	6 (21%)	1 (4%)	0.105
Haemostatic therapy				
PCC administration	31 (56%)	16 (55%)	15 (58%)	1.000
Mean PCC dosage	2019 ± 759	2088 ± 776	1947 ± 761	0.614
Tranexamic acid	3 (5%)	3 (10%)	0 (0%)	0.238
Transfusion blood products	8 (15%)	7 (24%)	1 (4%)	0.054
Neurosurgical procedures				
Hematoma evacuation	27 (49%)	9 (31%)	18 (69%)	0.007
EVD/ICP probe only	10 (18%)	3 (13%)	7 (25%)	0.164
None	18 (33%)	17 (59%)	1 (4%)	< 0.0001
Mortality				
In-hospital mortality	9 (16%)	5 (17%)	4 (15%)	1.000
30-day mortality	11 (20%)	7 (24%)	4 (15%)	0.510
3-months mortality	13 (24%)	8 (28%)	5 (19%)	0.537
1-year mortality	21 (38%)	14 (48%)	7 (27%)	0.164
3-year mortality	26 (47%)	16 (55%)	10 (38%)	0.282

INR: International normalized ratio; aPTT: activated partial thromboplastin time; GFR: glomerular filtration rate; GCS: Glasgow Coma Scale; PCC: prothrombin complex concentrates; EVD: external ventricular drain; ICP: intracranial pressure.
[a] Wilcoxon rank sum test.

admission, cases may have been misclassified if trauma was not reported or occurred > 24 h prior to hospital admission. It is also well-recognized that differentiation between chronic and acute subdural hematomas in computed tomography imaging can be difficult [8]. In our study, patients with traumatic DOAC-associated intracranial haemorrhage had a 1.4 fold higher three-year mortality rate than non-traumatic intracranial haemorrhage on DOAC treatment (55% vs. 38%). Although this finding has to be interpreted cautiously due to limited patient numbers, it may indicate that patients with traumatic intracranial haemorrhage have a higher risk for sustaining an unfavourable long-term course. Trauma itself may contribute to increased neuronal damage, but often patients with traumatic brain injury (TBI) on DOAC treatment also have severe comorbidities. Accordingly, patients with traumatic intracranial haemorrhage had lower platelet levels at hospital admission and also suffered more frequently from diabetes mellitus and impaired renal function in our study. It is well-established that severe comorbidities such as chronic kidney disease are associated with poor outcomes following intracranial haemorrhage [9]. Present comorbidities, trauma-related brain injury or a combination of both factors may contribute to unfavourable outcomes in these patients. A prospective study revealed higher death rates following TBI for at least 7 years compared to the general population [10]. Studies on the impact of DOAC treatment on short-term outcome parameters of TBI patients have shown conflicting results. Increased mortality rates in DOAC-treated TBI patients compared to TBI patients on VKA treatment have been reported in some studies [11], while others found no differences or even a more favourable outcome in DOAC-treated patients [12]. In the ageing population of industrialized countries, this issue is of high importance, as emergency physicians are increasingly encountered with TBI patients on DOAC treatment. In the United States, TBI-related emergency department visits of patients aged ≥75 years doubled from 2007 to 2013 [13]. The majority of respective TBI patients have

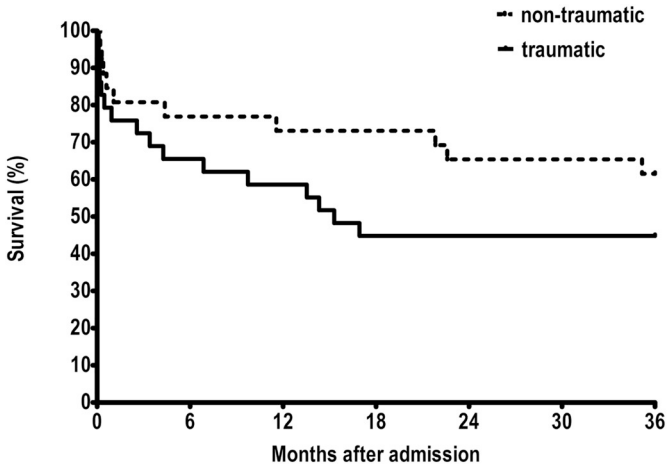

Fig. 1. Kaplan-Maier survival curves over three years in patients with non-traumatic intracranial haemorrhage (dotted line) and traumatic intracranial haemorrhage (black line).

suffered a low-level or same-level fall and anticoagulation therapy may convert minor haemorrhage into life-threatening haemorrhage. Furthermore, patients sustaining low-level and same-level falls frequently suffer from severe comorbidities that can have a negative impact on the further course. Treatment protocols for the acute management of patients with TBI on DOAC-treatment have to be optimized and risk factors for unfavourable long-term outcomes have to be identified. Furthermore, the role of trauma itself and the role of trauma-unrelated comorbidities in the further course of patients following traumatic intracranial haemorrhage on DOAC treatment should be further evaluated.

In conclusion, our findings may indicate that treatment with DOAC does not increase long term mortality of patients with intracranial haemorrhage. However, the impact of DOAC treatment in trauma patients with intracranial haemorrhage has to be characterized in future studies.

Conflicts of interest

C.B. has received consulting fees/speaker honoraria from Bayer Healthcare, Boehringer Ingelheim, CSL Behring and Tem International. O.W.S. has received speaker honoraria from CSL Behring. A.W.U. has no conflict of interest.

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