Impact of Oral Anticoagulation and Adenosine Diphosphate Inhibitor Therapies on Short-Term Outcome of Traumatic Brain Injury

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Abstract

Objective: Usage of oral anticoagulants (OAC) or adenosine diphosphate inhibitors (ADPi) is known to increase the risk of bleeding. We aimed to investigate the impact of OAC and ADPi therapies on short-term outcomes after traumatic brain injury (TBI).

Methods: All adult patients hospitalized for TBI in Finland during 2005–2018 were retrospectively studied using a combination of national registries. Usage of pharmacy-purchased OACs and ADPis at the time of TBI was analyzed with the pill-counting method (Social Insurance Institution of Finland). The primary outcome was 30-day case-fatality (Finnish Cause of Death Registry). The secondary outcomes were acute neurosurgical operation (ANO) and admission duration (Finnish Care Register for Health Care). Baseline characteristics were adjusted with multivariable regression including age, sex, comorbidities, skull or facial fracture, OAC/ADPi treatment, initial admission location, and the year of TBI admission.

Results: The study population included 57,056 persons (mean age 66 years) of whom 0.9% used direct oral anticoagulants (DOAC), 7.1% Vitamin K antagonists (VKA), and 2.3% ADPis. Patients with VKAs had higher case-fatality than patients without OAC (15.4% vs. 7.1%; adjHR 1.35, CI 1.23–1.48; p<0.0001). Case-fatality was lower with DOACs (8.4%) than with VKAs (adjHR 0.62, CI 0.44–0.87; p=0.005) and was not different from patients without OACs (adjHR 0.93, CI 0.69–1.26; p=0.634). VKA usage was associated with higher neurosurgical operation rate compared to non-OAC patients (9.1% vs. 8.3%; adjOR 1.33, CI 1.17–1.52; p<0.0001). There was no difference in operation rate between DOAC and VKA. ADPi was not associated with case-fatality or operation rate in the adjusted analyses. VKAs and DOACs were not associated with longer admission length compared with the non-OAC group, whereas the admissions were longer in the ADPi group compared with the non-ADPi group.

Conclusion: Preinjury use of VKA is associated with increases in short-term mortality and in need for ANOs after TBI. DOACs are associated with lower fatality than VKAs after TBI. ADPis were not independently associated with the outcomes studied. These results point to relative safety of DOACs or ADPis in patients at risk of head trauma and encourage to choose DOACs when oral anticoagulation is required.

Classification of evidence: This study provides Class II evidence that among adults with TBI, mortality was significantly increased in those using VKAs but not in those using DOACs or ADPis.

Introduction

Traumatic brain injury (TBI) in patients using oral anticoagulation (OAC) and adenosine diphosphate inhibitors (ADPi) has become increasingly common as the population ages.[1–3] Recent studies have shown direct anticoagulants (DOAC) to be noninferior and in some cases superior to Vitamin K antagonists (VKA) in reducing the risk of ischemic stroke in atrial fibrillation.[4–6] DOACs are also associated with better long-term outcomes compared to VKAs in patients with atrial fibrillation and ischemic stroke.[7] In patients without atrial fibrillation, ADPis appear superior to aspirin in secondary prevention of ischemic events, especially long-term.[8,9]

Patients with TBI who received OACs and ADPis prior to injury are at high risk for traumatic intracranial hemorrhage.[10,11] The incidence for intracranial hemorrhage in patients with mild TBI and OACs appears to be higher than previously thought.[12] Mild TBIs are common in older patients[13,14] who are at higher risk for atrial fibrillation and cardioembolic events. However, many studies that have examined the risk of intracranial hemorrhage and outcome in patients with TBI have not distinguished between patients taking OACs and ADPis.[15–17]

In a recent systematic review and meta-analysis, preinjury OACs were associated with significantly higher overall and in-hospital mortality, but not with the need for acute neurosurgical operations (ANO) compared to TBI patients without OACs.[18] Mortality rates and the need for ANOs seems to be quite similar between VKAs and DOACs after TBI[19], although conflicting results in favor of DOACs have been presented.[20,21] ADPis do not appear to be associated with increased mortality after TBI in single-center studies.[22,23]

The current literature remains nebulous due to the lack of large-scale studies in terms of outcome of TBI in patients on OACs and ADPis. Furthermore, given the growing ageing population at increased risk for TBI and the increasing prescription of agents that affect blood clotting, it is important to have clear indications for different OACs and ADPis for this subset of patients. Herein, we used a large nationwide cohort to examine whether OAC and ADPi therapies have differential impact on short-term outcomes, primarily mortality, after TBI.

Materials and methods

Patients

All ward admissions with TBI (ICD-10 codes S06.* as the primary diagnosis) for patients aged ≥18 years in Finnish hospitals and healthcare ward units between January 1, 2005 and December 31, 2018 were retrospectively collected from the Care Register for Health Care (CRHC). This mandatory by law database held by the National Institute for Health and Welfare (THL), Helsinki, Finland captures all health care ward discharges in Finland and includes information on performed surgical operations. Transfers between and within healthcare providers related to a particular admission episode were combined as one admission. Study included data from 338 hospitals or other health care units treating TBI, 5 of which provide neurosurgery services. The first admission of each patient during the study period was included. Patients with operated chronic subdural hematoma (ICD-10 codes S06.5 or I62.0 with operation for evacuation of chronic subdural hematoma [operational codes AAD10 or AAD12]) were not included in the study. Patients with missing follow-up data (n=485) were excluded. The primary outcome of interest was death within 30 days after TBI admission. The secondary outcomes were an ANO and admission duration.

Validity of the ICD-10 TBI codes were studied by reviewing patient records of randomly selected patients corresponding to our inclusion criteria with S06.* as the primary discharge diagnosis admitted to the Turku University Hospital, Turku, Finland, and the North Karelia Central Hospital, Joensuu, Finland. Of 300 reviewed patients, 294 patients fulfilled the diagnostic criteria for S06.* resulting in a positive predictive value of 0.98.

Definitions

Pharmacy purchases of anticoagulation and ADPi medications within 90 days prior to TBI admission were recognized using ATC-codes (Supplement Table 1). OACs and ADPi are only available from pharmacies by prescription in Finland, while aspirin is available as over the counter medication. The daily pill counting method based on standardized defined daily dose (DDD) (Supplement Table 1) was used to estimate the usage of prescribed medication at the day of TBI. OAC therapy was classified as DOAC or VKA based on the latest OAC purchase, and ADPi therapy was classified as Clopidogrel or Prasugrel/Ticagrelor based on the latest ADPi purchase. Patients with purchase of parenteral anticoagulants without OAC purchase were excluded (n=421). Patients who purchased OAC within 90 days prior to TBI, but in whom the duration of purchased OACs did not cover the day of TBI were excluded (Figure 1). Skull or facial fracture was defined as ICD-10 diagnosis S02.* as co-diagnosis. Comorbidities were detected from the combination of included registries.[24] ANOs were detected as previously defined.[25] Admission duration included ward and hospital transfers.

Standard Protocol Approvals, Registrations, and Patient Consents

The CRHF Registry and Finnish Cancer Registry data were obtained from the National Institute for Health and Welfare of Finland / Findata (permission no: THL/2245/5.05.00/2019). Fatality data were obtained from a nationwide cause of death registry held by Statistics Finland (permission no: TK-53-484-20). Prescription medication purchase data (including ATC codes, strength and amount, and purchase dates) and drug reimbursement permission data were obtained from the Social Insurance Institution of Finland (permission no: 91/522/2015). The collection and reporting of data within the included registries are mandated by law; therefore, the data from these registries provides a full picture of the Finnish population. Follow-up data was complete for all included patients. Because this was a retrospective nationwide registry study, the requirements for permissions from individual hospital review boards and informed consent were waived by the law and participants were not contacted. The data underlying this article were provided by the Findata by permission. The Data is available from Findata (findata.fi) by permission. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679, Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6).

Statistical methods

Baseline features were analyzed with Chi-squared test or ANOVA as appropriate. Case fatality was analyzed with the Kaplan-Meier method, log-rank test, and adjusted Cox-regression. Proportional hazard assumptions were examined with Schoenfeld residuals. ANOs were analyzed with logistic regression. Admission duration was analyzed with linear regression (log-transformed and standardized dependent variable). Regression analyses were adjusted with age, sex, co-morbidities listed in Table 1 (except for atrial fibrillation), skull or facial fracture, OAC/ADPi treatment, and initial admission location and stratified by the year of TBI admission. Potential modulative influence of combined OAC and ADPi therapies were studied with interaction analysis in adjusted regression models. Potential interaction of age (≤65 or

>65 years) with association between OAC and ADPi and case-fatality was also studied. The results are given as the mean, median, percentage, hazard ratio (HR), or odds ratio (OR) with a 95% confidence interval (CI), interquartile range (IQR), or ± SD. Statistical significance was inferred at p value < 0.05. Analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

The total study population included 57,056 patients with TBI, of whom 0.9% were treated with DOAC and 7.1% with VKA. Warfarin was the only oral VKA used by the study patients. The mean age of all study patients was 66.0 (SD: 21.3, range: 18-105) years and 55.6% were men. Patients with OAC were older, more often female, and had higher comorbidity burden compared to TBI patients without OAC (Table 1). Initial admission location was more frequently local health center than hospital with surgical capability in patients with OAC treatment. Patients receiving DOAC were more often women and more likely to have a history of alcohol abuse than patients receiving VKA (Table 1). The most common recorded primary TBI diagnosis was concussion / mild TBI (Supplement Table 2). There was no difference in the proportion of skull or facial fractures between the OAC regimens. Of 527 DOAC patients, 125 (23.7%) used Dabigatran and 402 (76.3%) used Factor Xa inhibitors (FXai; apixaban, edoxaban, rivaroxaban). An ADPi was used by 2.3% of study patients. Clopidogrel was used by 95.8% and Ticagrelor or Prasugrel by 4.2% of the ADPi users. All patients receiving both OAC and ADPi were taking Clopidogrel. Patients taking ADPi were older and had a higher rate of comorbidities than patients not taking ADPi (Table 2). Patients taking either OAC or ADPi had a lower frequency of skull or facial fractures than patients not taking OAC (Table 1) or ADPi (Table 2).

Case-fatality

Of all TBI patients, 4,369 died within 30 days. The 30-day case-fatality rate was 8.4% in the DOAC group, 15.4% in the VKA group, and 7.1% in the non-OAC group (Figure 2). Case-fatality in patients treated with DOAC did not differ from that in patients not treated with OAC in either the non-adjusted (p=0.263) or the multivariable adjusted analysis (adjHR 0.93; CI 0.69–1.26; p=0.634). Patients treated with VKA had a higher risk of dying within 30 days after TBI compared to non-OAC patients in both the non-adjusted (p < 0.0001) and multivariable adjusted analyses (adjHR 1.35; CI 1.23–1.48; p<0.0001). Patients treated with DOAC had lower case-fatality than patients treated with VKA in both the unadjusted (p < 0.0001) and adjusted analyses (adjHR 0.62; CI 0.44–0.87; p=0.005). The case fatality was 6.4% in the Dabigatran group and 9.7% in the FXai group (non-adjusted p=0.048) with adjHR of 0.33 (CI 0.11–0.94; p=0.039). The 30-day case fatality rate was 10.2% in the ADPi group and 7.6% in the non-ADPi group (non-adjusted p=0.0004) (Figure 3). ADPis were not associated with case-fatality in the multivariable model (adjHR 0.89; CI 0.74–1.06; p=0.194). There were no interactions between OAC and ADPi therapies (interaction p=0.524) or between age and OAC (interaction p=0.905) or ADPi (interaction p=0.270) in analysis of case-fatality. Case-fatality was 9.4% in patients taking clopidogrel and 20.0% in patients taking prasugrel/ticagrelor (non-adjusted p=0.008; adjHR 1.74; CI 0.84–3.60; p=0.134). The underlying cause of death was determined to be external in 81.1% and disease in 18.9% of the deceased patients with falls being the most common mechanism of trauma (Supplement Table 3). Underlying causes of death did not differ between study groups. Association of baseline features with case-fatality are presented in Supplement Table 4. Of comorbidities, coagulopathy, liver disease, and heart failure were associated with the highest risk of case-fatality. Patients treated in the university hospitals had over five-fold risk of death compared with patients treated in the health centers.

Acute neurosurgical operations

ANO was performed to 4,770 patients with TBI. The ANO rate was 4.7% in the DOAC group, 9.1% in the VKA group, and 8.3% in the non-OAC group (non-adjusted p=0.003). Patients with VKA had higher odds for ANO than patients without OAC (adjOR 1.33; CI 1.17–1.52; p < 0.0001). Adjusted odds for ANOs did not differ between the DOAC vs. VKA groups (adjOR 0.90; CI 0.55–1.47; p=0.126) or between the DOAC vs. non-OAC groups (adjOR 1.08; CI 0.70–1.66; p=0.110). Of patients using Dabigatran, 4.8% and of those using an FXai, 4.7% underwent ANO (adjOR 1.15; CI 0.36–3.73; p=0.300). ANOs were performed in 6.5% of patients treated with ADPi and in 8.4% of patients not treated with ADPi (adjOR 0.93; CI 0.73–1.18; p=0.542). There was no interaction between OAC and ADPi therapies (interaction p=0.739). The rate of surgery was 6.2% in patients treated with clopidogrel and 12.7% in patients treated with prasugrel/ticagrelor (adjOR 2.31; CI 0.79–6.77; p=0.128).

Admission duration

The median length of all TBI admissions was four days (IQR 2–11 days). The median duration was four days (IQR 2–11) in the DOAC group, five days (IQR 2–15) in the VKA group, and three days (IQR 2–10) in the non-OAC group. Admission duration did not differ between patients treated with DOAC and patients without OAC in non-adjusted (p=0.328) or multivariable adjusted (p=0.354) analyses. Treatment with VKA was associated with longer admission in the non-adjusted analysis (p<0.0001), but not after multivariable adjustments (p=0.738). The median duration was five days (IQR 2–12) in the ADPi group and four days (IQR 2–10) in the non-ADPi group with p<0.0001 in the non-adjusted and p=0.0003 in the adjusted analyses. There was no interaction between OAC and ADPi therapies (interaction p=0.182).

Classification of evidence

This study provides Class II evidence that among adults with TBI, mortality was significantly increased in those using VKAs but not in those using DOACs or ADPis.

Discussion

This was a nationwide population-based study examining the impacts of OAC and ADPi therapies on short-term outcome after TBI. The main findings from the adjusted analyses are: i) case-fatality was higher with VKA than without OACs, ii) case-fatality was lower with DOACs than with VKA, iii) case-fatality was similar with DOACs and without OACs, iv) case-fatality was similar with ADPis and without ADPis, v) odds ratio for ANOs was higher with VKA than without OACs, vi) odds ratio for ANOs was similar with DOACs and without OACs, and vii) odds ratio for ANOs was similar with ADPis and without ADPis Other findings were: i) in terms of DOACs, case-fatality was higher with FXais than Dabigatran, and ii) case-fatality was similar between ADPi types.

The global population ages: In 2015, people aged ≥60 years of age made up 12% of the world's population, and this number is expected to reach 22% by 2040. In Europe, 24% of the population is already aged ≥60 years and that proportion is projected to reach 34% in 2050.[26] Older adults are at higher risk for atrial fibrillation and cardioembolic events, but they are also at higher risk for TBIs.[13,14,27] The major concern in patients taking medications that affect blood clotting who suffer a TBI is the increased risk of intracranial hematoma expansion and mortality. Studies examining outcome after mild TBI in patients with DOACs and VKAs reported lower mortality associated with DOAC use. In these two studies, patients did not have major intracranial hemorrhage and patients receiving DOACs did not have reversal of anticoagulation, whereas most patients receiving VKAs were treated with Vitamin K.[28,29]

With respect to TBIs of all severities, the evidence is not so consistent. Two recent prospective and one retrospective study reported that VKA and DOAC users had comparable mortality rates after a TBI.[19,22,30] In another recent study that included patients with all severities of TBI, there was no statistically significant difference in the expansion rates of intracranial hematomas between VKAs and DOACs. Nonetheless, DOAC-treated patients had better outcomes compared to patients receiving VKAs despite the low use of reversal strategies.[31] Conflicting results have also been reported. A single-center study reported a higher rate of hematoma expansion in patients with traumatic intracerebral hematomas, higher rate in need for ANOs and higher mortality on DOACs compared with VKAs.[32] However, a recent systematic review and meta-analysis including 2,622 patients of whom 239 were on DOACs and 524 on VKA found that in-hospital mortality and the need for ANOs did not differ between TBI patients on DOACs and VKAs. The authors noted that within each study, surgery rates, reversal agents used, hematoma progression, and in-hospital mortality differed significantly between DOAC and VKA cohorts.[21] A recent study published after the above-mentioned review article reported that OAC use was associated with enlargement of intracranial hematomas, whereas use of antiplatelet agents was not when compared with patients without medications affecting blood clotting.[33]

Our large-scale study of 57,056 patients with TBI, of whom 527 patients received DOACs and 4,053 patients received VKAs, brings clarity to the issue: patients who received VKAs before the injury have twice the mortality rate of patients who received DOACs, who in turn have a similar mortality rate to patients who did not take OACs. Dabigatran was found to be associated with lower mortality than FXais. It is noteworthy that in a Norwegian study examining risk of intracranial hemorrhage associated with antithrombotic therapy, it was observed that all other antithrombotic therapies excluding Dabigatran were associated with increased risk of hemorrhage.[34] In this study, patients receiving VKA had higher odds for ANO than patients without OAC. However, we found no odds ratio differences for ANOs between the DOAC vs. VKA groups or between the DOAC vs. non-OAC groups. The current results are largely consistent with previous findings on the impact of ADPis on mortality after TBI.[17,22,23] We also found that the odds ratio for ANOs was similar in patients who received ADPis before injury and patients without ADPis. In addition, we did not find any interaction between the impacts of OAC and ADPi therapies on mortality and ANOs. Intriguingly, however, VKAs and DOACs were not associated with longer admission length compared with the non-OAC group, whereas the admissions were longer in the ADPi group compared with the non-ADPi group.

We used the need for ANOs and admission lengths as surrogate markers of TBI severity. When examining factors associated with case-fatality, we identified many comorbidities but also treatment at the university hospitals compared with health centers. This reflects the fact that most severe TBI cases are treated in centers where neurosurgical services are available.

We observed that patients who received DOAC were more often women. In another recent study, it was reported that women outnumbered men in patients who received DOAC and suffered a TBI.[35] The observation in the current study may be related to the results of our previous study, in which we found that the number of TBIs among elderly women in Finland increased during partially the same years as in this study. In addition, DOACs were introduced into general practice around the same time as the CHA_2DS_2VASc score[36], which gives an additional risk point to women. This may have influenced the gender distribution of DOAC patients in Finland.

There are several strengths in this study. We have included all Finnish hospitals that provide facilities for TBI patient follow-up and all tertiary care hospitals providing neurosurgical services. We used multiple national registries that provide

a full picture of the Finnish population. The collection and reporting of data within the included registries are mandated by law. An important limitation is the possibility of selection bias, as we included only admitted TBI patients. Patients with OAC or ADPi may be more likely to be admitted to ward for monitoring after minor head trauma than patients without OAC, possibly resulting in less severe injuries in the treated groups. This could dilute the observed results, notwithstanding the fact that adjustments were made for skull or facial fractures. However, it is unlikely that this potential bias would affect the DOAC and VKA groups differently. Actual medication usage use was not confirmed separately; we used a standard method of prescription medication purchase to study usage.[37] Aspirin is mostly used as over the counter drug and we could not assess its usage in the study population. We did not assess the use of OAC reversal strategies. However, the favorable impact of DOACs on mortality after TBI remains strong, because i) the Finnish national TBI care guideline advocates the use of Vitamin K for VKA reversal[38], ii) the antidote Idarusitsumab for Dabigatran was not authorized in Finland until late 2015 and iii) the antidote Andexanet alfa for FXA was authorized after the end of the current data collection in 2019. Because of the limitations of the ICD-10 coding system, TBIs with hemorrhagic intracranial lesions cannot be reliably distinguished from diffuse and non-hemorrhagic TBIs—especially in cases with multiple lesion types on head computed tomography.

As a final limitation of the study, we must acknowledge the lack of data examining stroke rates in different groups of patients with TBI. The use of OACs or ADPis is a compromise between thrombosis and bleeding. The majority of the study patients on OACs had atrial fibrillation and a number of other known risk factors for stroke. In patients with risk factors for thrombosis and thromboembolic events, the use of OACs and ADPis is advocated, but the current results highlight the importance of preventive measures to reduce the risk of head trauma, particularly in patients taking OACs.

Conclusion

We found that VKA use is associated with increased short-term mortality and need for of ANOs after TBI. DOACs are associated with lower fatality than VKAs after TBI and case-fatality is similar with DOACs and without OACs. ADPis are not associated with mortality or need for ANOs after TBI. The results reinforce the safety of DOACs and ADPis in patients at risk of head trauma and encourage the use of DOACs when oral anticoagulation is required.

Figure Legends

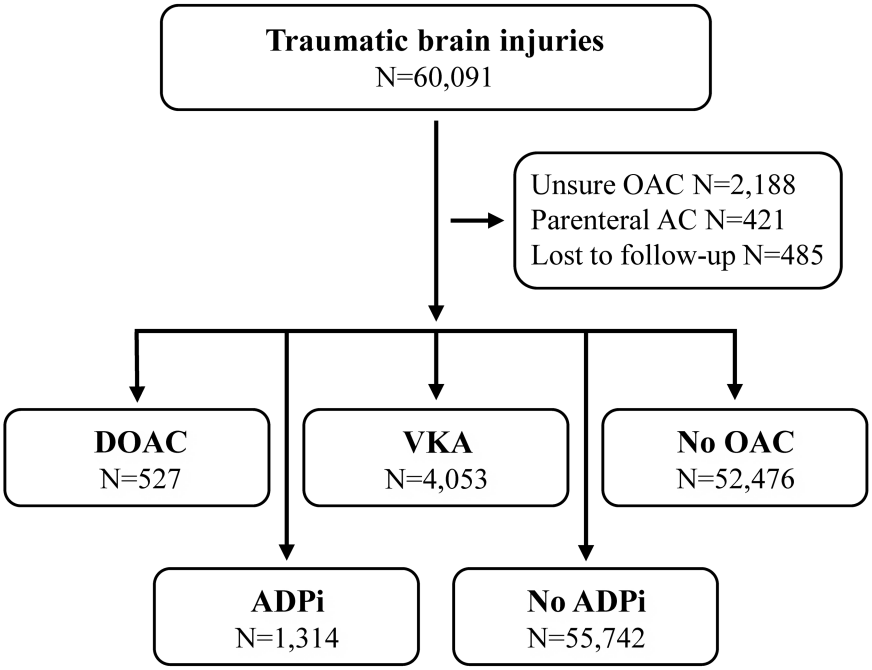

Figure 1. Study flow-chart. ADPi, adenosine diphosphate inhibitor; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

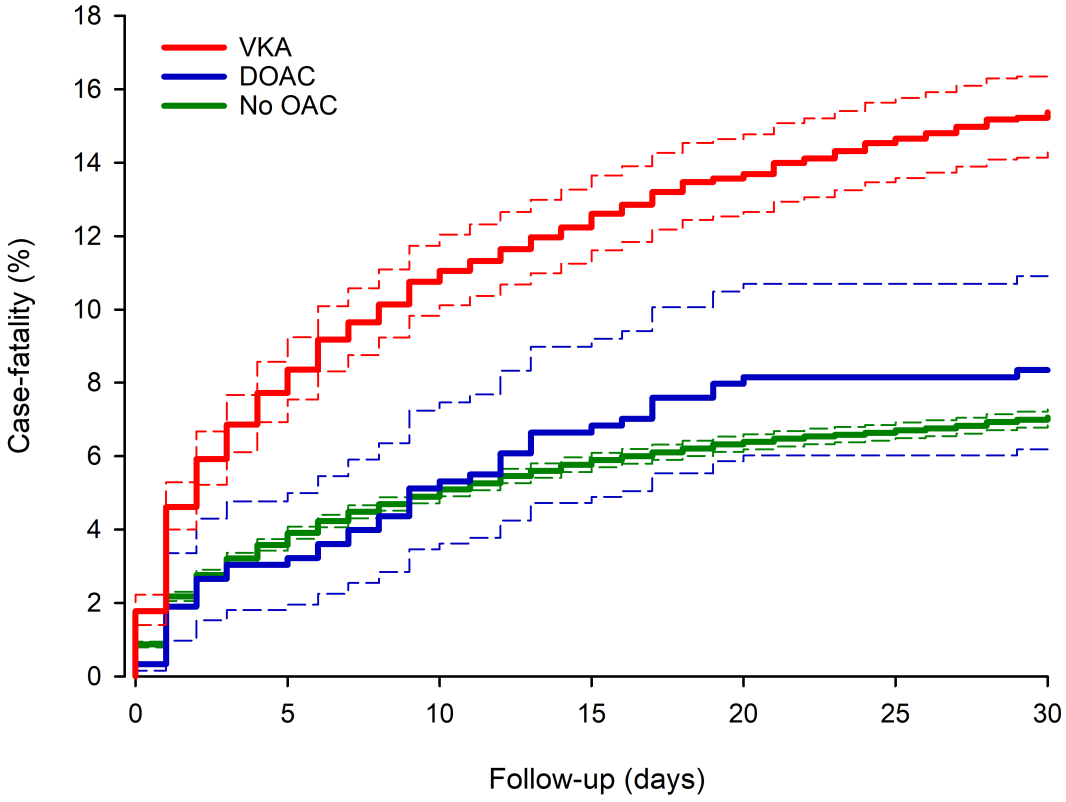

Figure 2. Short-term case-fatality after traumatic brain injury by usage of oral anticoagulation. Dashed lines represent 95% confidence intervals. DOAC, direct oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

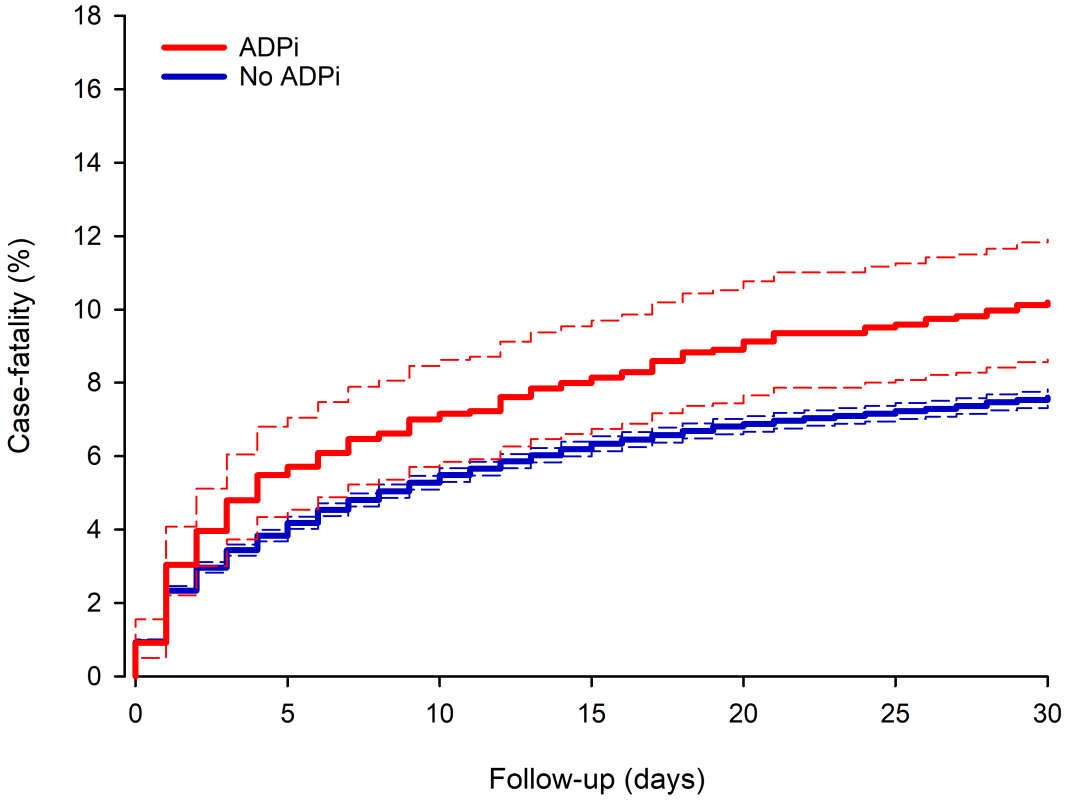

Figure 3. Short-term case-fatality after traumatic brain injury by usage of adenosine diphosphate inhibitor. Dashed lines represent 95% confidence intervals. ADPi, adenosine diphosphate inhibitor

Table 1. Baseline features of traumatic brain injury patients with direct oral anticoagulants (DOAC), vitamin K-antagonists (VKA), or no oral anticoagulation therapy (OAC).

Variable	DOAC N=527	VKA N=4,053	No OAC N=52,476	Between group P-value	DOAC vs. VKA P-value
Age, years (SD)	79.8 (9.3)	78.9 (10.1)	61.4 (21.4)	<0.0001	0.069
Male	42.7%	51.0%	56.1%	<0.0001	0.0003
Co-morbidity history					
Alcohol abuse	10.3%	6.5%	16.5%	<0.0001	0.0002
Atrial fibrillation	94.9%	71.1%	9.4%	<0.0001	<0.0001
Cerebrovascular disease	37.0%	34.9%	17.4%	<0.0001	0.339
Chronic pulmonary disease	23.3%	16.7%	11.4%	<0.0001	0.0002
Coagulopathy	1.7%	1.3%	0.7%	<0.0001	0.486
Dementia	21.3%	17.7%	10.5%	<0.0001	0.049
Diabetes	27.9%	26.9%	13.6%	<0.0001	0.635
Drug abuse	1.3%	0.4%	2.4%	<0.0001	0.019
Heart failure	35.9%	38.7%	9.4%	<0.0001	0.214
Heart valve disease	11.6%	15.4%	3.2%	<0.0001	0.021
Hypertension	68.5%	62.5%	32.2%	<0.0001	0.007
Liver disease	3.0%	1.6%	3.0%	<0.0001	0.019
Malignancy	24.5%	21.7%	10.4%	<0.0001	0.142
Myocardial infarction	13.7%	14.4%	5.8%	<0.0001	0.645
Paralysis	1.5%	0.9%	0.8%	0.138	0.209
Peripheral vascular disease	9.9%	9.6%	3.3%	<0.0001	0.858
Psychotic disorder	4.6%	5.1%	6.2%	0.010	0.585
Rheumatic disease	9.5%	6.7%	4.5%	<0.0001	0.020
Renal failure	3.8%	4.3%	1.7%	<0.0001	0.593
Skull or facial fracture	4.2%	3.6%	8.9%	<0.0001	0.511
Adenosine diphosphate inhibitor	0.8%	1.0%	2.4%	<0.0001	0.813
Admission location				<0.0001	0.011
University hospital	20.9%	26.6%	32.1%		
Other hospital	38.5%	37.6%	43.3%		
Health center	40.6%	35.8%	24.6%		

DOAC, direct oral anticoagulant; VKA, vitamin K-antagonist (VKA); No OAC, no oral anticoagulation therapy

Table 2. Baseline features of patients with traumatic brain injury with and without adenosine diphosphate inhibitors

Variable	ADPi N=1,314	No APDi N=55,742	P-value
Age, years (SD)	77.1 (11.1)	62.5 (21.3)	<0.0001
Male	49.9%	55.7%	<0.0001
Co-morbidity history			
Alcohol abuse	9.3%	15.9%	<0.0001
Atrial fibrillation	14.1%	14.6%	0.628
Cerebrovascular disease	65.8%	17.7%	<0.0001
Chronic pulmonary disease	19.3%	11.7%	<0.0001
Coagulopathy	1.0%	0.8%	0.356
Dementia	16.8%	11.0%	<0.0001
Diabetes	32.2%	14.2%	<0.0001
Drug abuse	1.3%	2.3%	0.019
Heart failure	22.5%	11.4%	<0.0001
Heart valve disease	7.1%	4.1%	<0.0001
Hypertension	68.6%	33.9%	<0.0001
Liver disease	0.9%	3.0%	<0.0001
Malignancy	20.2%	11.1%	<0.0001
Myocardial infarction	35.3%	5.8%	<0.0001
Paralysis	2.1%	0.8%	<0.0001
Peripheral vascular disease	15.5%	3.5%	<0.0001
Psychotic disorder	6.0%	6.1%	0.945
Rheumatic disease	8.2%	4.6%	<0.0001
Renal failure	4.9%	1.8%	<0.0001
Skull or facial fracture	5.4%	8.5%	<0.0001
Oral anticoagulation	3.3%	8.1%	<0.0001
Admission location			<0.0001
University hospital	25.5%	31.8%	
Other hospital	38.3%	42.9%	
Health center	36.2%	25.3%	

ADPi, adenosine diphosphate inhibitors

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