Pharmaceutical Venous Thrombosis Prophylaxis in Critically Ill Traumatic Brain Injury Patients

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Abstract
The aims of this study are to describe the use of pharmaceutical venous thromboembolism (pVTE) prophylaxis in patients with traumatic brain injury (TBI) in Europe and study the association of pVTE prophylaxis with outcome. We included 2006 patients ≥18 years of age admitted to the intensive care unit from the CENTER-TBI study. VTE events were recorded based on clinical symptoms. Variation between 54 centers in pVTE prophylaxis use was assessed with a multi-variate random-effect model and quantified with the median odds ratio (MOR). The association between pVTE prophylaxis and outcome (Glasgow Outcome Scale-Extended at 6 months) was assessed at center level with an instrumental variable analysis and at patient level with a multi-variate proportional odds regression analysis and a propensity-matched analysis. A time-dependent Cox survival regression analysis was conducted to determine the effect of pVTE prophylaxis on survival during hospital stay. The association between VTE prophylaxis and computed tomography (CT) progression was assessed with a logistic regression analysis. Overall, 56 patients (2%) had a VTE during hospital stay. The majority, 1279 patients (64%), received pVTE prophylaxis, with substantial between-center variation (MOR, 2.7; \( p < 0.001 \)). A moderate association with improved outcome was found at center level (odds ratio [OR], 1.2 [0.7–2.1]) and patient level (multi-variate adjusted OR, 1.4 [1.1–1.7], and propensity adjusted OR, 1.5 [1.1–2.0]), with similar results in subgroup analyses. Survival was higher with the use of pVTE prophylaxis (\( p < 0.001 \)). We found no clear effect on CT progression (OR, 0.9; CI [0.6–1.2]). Overall, practice policies for pVTE prophylaxis vary substantially between European centers, whereas pVTE prophylaxis may contribute to improved outcome.

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Trial registration number is NCT02210221 at ClinicalTrials.gov, registered on August 6, 2014 (first patient enrollment on December 19, 2014).

Keywords: intensive care units; traumatic brain injuries; venous thrombosis

Introduction
Prevention of venous thromboembolism (VTE) is less straightforward in patients with traumatic brain injury (TBI), compared to non-neurological patients admitted to the intensive care unit (ICU), because clinicians have to weigh the risks of progression of cerebral hemorrhage against the risks of VTE.1 Besides, compared to trauma patients, some studies suggest that patients with TBI might be at higher risk of developing VTE.2,3

Guidelines for patients with TBI lack high-level recommendations regarding the use of pharmaceutical VTE (pVTE) prophylaxis in patients with severe TBI, and randomized controlled trials (RCTs) on the effectiveness of pVTE prophylaxis are scarce.4,5 This lack of high-level evidence could result in substantial variation in pVTE prophylaxis practices. Previous studies reported wide variation in incidence rates of deep venous thrombosis (DVT) and pulmonary embolism (PE),6 but more recent studies suggest that the incidence rates of clinical VTE are low.7 When incidences of VTE are indeed low, this raises the question of whether patients with brain injuries should be given pVTE prophylaxis, especially in the acute phase during ICU care when risk of progression of intracranial hemorrhage is substantial. Previous studies have yielded conflicting results on the effectiveness and safety of pVTE prophylaxis.8–11 However, these studies often focus on computed tomography (CT) progression or VTE incidence alone, as opposed to long-term outcome.

The primary aim of this study is to describe the use of pVTE prophylaxis in ICU patients with TBI in European neurotrauma centers, and the secondary aim is to study the association of pVTE prophylaxis with outcome.

Methods
CENTER-TBI study
This study is part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, in which 54 ICUs from 18 countries in Europe and Israel participated.12 Criteria to enroll a patient in the CENTER-TBI study were 1) a clinical diagnosis of TBI, 2) indication for a head CT, and 3) presentation within 24 h after initial trauma. The single exclusion criterion was a previous history of neurological disease that could interfere with clinical outcome assessment. A more extensive description of the study and patient characteristics can be found in previous publications.12,13 The CENTER-TBI study included patients in three strata: emergency room (emergency department; ED), ward, and ICU. Inclusion criteria for the current analysis selected patients from the CENTER-TBI Core study who were 1) admitted to the ICU upon presentation and 2) older than 18 years. Ethics approval was obtained at each participating site. Consent for study participation was obtained according to local legislation from patient, legal representative, or next of kin, for all patients recruited.14

Pharmaceutical prophylaxis
Detailed data on VTE prophylaxis were collected. Both the start and duration of pVTE prophylaxis were recorded, as well as the type of drug for pharmaceutical prophylaxis. Use of pVTE prophylaxis in this study was defined in two ways: 1) any use of pharmaceutical DVT prophylaxis at any time during the entire hospital stay and 2) use of pharmaceutical DVT prophylaxis during ICU stay.

Outcomes
The presence of a DVT or PE during hospital admission was recorded based on clinical symptoms as per clinical practice (without routine leg ultrasound in all patients). The Glasgow Outcome Scale-Extended (GOSE) at 6 months and CT progression were the primary outcome measures. CT progression was recorded by clinicians during ICU and later hospital stay.

Statistical analyses
Baseline characteristics are described for patients primarily admitted to the ICU with and without pVTE
prophylaxis. Group differences were determined with chi-square tests for categorical variables and analysis of variance for continuous variables.

To answer the primary aim (the variation in the use of pVTE between European ICUs), a multi-variate model with pharmaceutical VTE prophylaxis as outcome and a random effect for center were used to quantify between-center variation using the median odds ratio (MOR),\textsuperscript{15} which was further illustrated using caterpillar plots. To quantify between-country variation, an adjusted random-effects model at country level was used and illustrated in a map of Europe. The higher the random effect, the more likely a country was to use pVTE prophylaxis, even after correction for case-mix severity and random variation.

To answer the secondary aim (the effect of pVTE prophylaxis on long-term outcome), various statistical analyses were performed; at patient level, at center level, and a survival analysis. To assess the effects of pVTE prophylaxis on 6-month outcome, several analytical approaches were used at patient and center level. At patient level, an unadjusted proportional odds model was applied to assess the uncorrected relation between the use of pVTE prophylaxis and ordinal GOSE. To correct for confounding, the following variables were added: age, pupils, motor, hypotension, hypoxia, epidural hematoma (EDH), traumatic subarachnoid hemorrhage (tSAH), Marshall, Injury Severity Score (ISS), first glucose, first hemoglobin, presence of a central venous catheter, invasive blood pressure monitoring, comorbidity, American Society of Anesthesiologists (ASA), past anticoagulant use, use of tranexamic acid at the ED or ICU, cranial surgery, and extracranial surgery. We conducted multi-variate proportional odds regression analysis using these covariates, a random effect for center, and 6-month outcome. In addition, we also undertook a time-dependent Cox survival analysis. This Cox survival model with pVTE as a time-dependent covariate has two features. First, it only uses data when the patient is still “at risk” of receiving pVTE (i.e., in the hospital). Second, it takes into account the timing of pVTE, that is, patients switch from control to intervention group on the exact day they receive pVTE prophylaxis. This model was corrected using the same confounders as described above (age, pupils, motor, hypotension, hypoxia, EDH, tSAH, Marshall, ISS, first glucose, first hemoglobin, presence of a central venous catheter, invasive blood pressure monitoring, comorbidity, ASA, past anticoagulant use, and use of tranexamic acid).

A logistic regression model was used to study the effect of pVTE prophylaxis on CT progression, corrected for the confounders as described above. In addition, we studied the effect of various drugs for pVTE prophylaxis on 6-month outcome, using a multi-variate proportional odds regression, corrected for the confounders as described above. For this analysis, parnaparin, tinzaparin, heparin, and low-molecular-weight heparin (LMWH) were combined in an “other” category.

R statistical software was used for analyses. Missing data were imputed with the mice package.\textsuperscript{16} Data were extracted from Neurobot (version 2.1).
Results

A total of 4509 patients participated in the CENTER-TBI study. Of these, 2006 adult patients were included in the ICU stratum. The majority of these patients received pharmaceutical VTE ($N=1279; 64\%$) whereas around one third received no pVTE prophylaxis ($N=672; 34\%$). Most patients received pVTE prophylaxis during ICU stay ($N=1171$), and in a minority of patients ($N=108$), pVTE prophylaxis was started after ICU stay (Fig. 1).

Mechanical VTE prophylaxis was applied in around half of the cases that received pVTE prophylaxis ($N=657; 53\%$) and only in a minority with no pVTE prophylaxis ($N=193; 29\%$; Table 1).

**FIG. 1.** Flowchart patient inclusion in current study. Flowchart of the use of pVTE prophylaxis at ICU stay or not, including missing values. CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; ICU, intensive care unit; VTE, venous thrombotic event.
Baseline characteristics

Patients who sustained more severe injuries, based on the Glasgow Coma Scale (GCS) and ISS, were more likely to receive pVTE prophylaxis. Groups were similar regarding age and sex. A substantial proportion of patients with severe TBI received no pharmaceutical DVT prophylaxis (N = 272; 43%). We found no significant differences in brain injuries on CT between the pVTE and non-pVTE groups, except more contusions in the pVTE group. Factors increasing the likelihood for VTE were central venous catheter, invasive blood pressure monitoring, cranial surgery, use of tranexamic acid, and a history of a cardiac event. Length of stay in the ICU and hospital was significantly shorter in the pVTE group.

Table 1. Baseline Characteristics in All ICU Admitted Patients

| N = 1951 | No pVTE prophylaxis | pVTE prophylaxis | p value | No pVTE prophylaxis at the ICU | N = 1279 | p value | Received pVTE prophylaxis at the ICU | N = 1171 | p value |
|----------|---------------------|------------------|---------|--------------------------------|----------|---------|--------------------------------|----------|---------|
| Age (median, IQR) | 52 [33–68] | 51 [33–65] | 0.266 | 53 [34–68] | 51 [32–64] | 0.031 |
| Sex, male (N, %) | 485 (72.2) | 950 (74.3) | 0.343 | 564 (72.3) | 871 (74.4) | 0.335 |
| Mechanical DVT prophylaxis | 193 (28.8) | 657 (53.4) | <0.001 | 251 (33.3) | 599 (53.2) | <0.001 |
| ISS (median, IQR) | 26 [17–41] | 32 [25–43] | <0.001 | 26 [18–38] | 33 [25–43] | <0.001 |
| GCS (N, %) | Mild | 270 (42.3) | 382 (31.3) | <0.001 | 316 (42.3) | 336 (30.2) | <0.001 |
| CT (N, %) | tSAH | 435 (73.5) | 832 (75.1) | 0.504 | 505 (73.4) | 762 (75.3) | 0.410 |
| Pre-injury ASA (N, %) | Normal healthy | 363 (57.4) | 682 (55.4) | 409 (55.5) | 636 (56.5) |
| Cause of injury (N, %) | Road traffic incident | 247 (38.0) | 582 (47.1) | 299 (39.7) | 530 (46.8) |
| General VTE risk factors (N, %) | BMI >25 | 275 (55.7) | 554 (52.7) | 322 (55.5) | 507 (52.5) |
| General VTE risk factors (N, %) | <0.001 | | | | |
| BMI >25 | 275 (55.7) | 554 (52.7) | 322 (55.5) | 507 (52.5) |
| History of VTE | 4 (0.6) | 15 (1.2) | 0.321 | 6 (0.8) | 13 (1.1) |
| Central venous catheter | 207 (31.1) | 586 (45.9) | <0.001 | 244 (31.6) | 549 (46.9) |
| Invasive bp monitoring | 488 (72.9) | 1127 (88.2) | <0.001 | 575 (74.0) | 1040 (88.9) |
| Cranial surgery | 201 (30.0) | 562 (44.2) | <0.001 | 246 (31.7) | 517 (44.5) |
| Extracranial surgery | 105 (15.7) | 451 (35.5) | <0.001 | 129 (16.6) | 427 (36.7) |
| Length of ICU stay | 2 [1–6] | 10 [4–14] | <0.001 | 2 [1–6] | 11 [4–19] |
| Length of hospital stay | 7 [3–14] | 20 [11–36] | <0.001 | 8 [3–17] | 21 [11–37] |
| Past medication (N, %) | Anticoagulants | 35 (5.6) | 63 (5.2) | 44 (6.1) | 54 (4.9) |
| PAI | 64 (10.2) | 126 (10.4) | 81 (11.2) | 109 (9.9) |
| Both | 5 (0.8) | 11 (0.9) | 6 (0.8) | 10 (0.9) |

This table shows the baseline characteristics of TBI patients admitted to the ICU stratified by the use of pharmaceutical DVT prophylaxis (at any time during the stay).

aBecause a Marshall score of V rarely occurred, scores V and VI are condensed.
bCardiac (arrhythmia, valvular heart disease, congenital heart disease, thromboembolic heart disease, and ischemic heart disease), renal (renal insufficiency or failure), oncological, hepatic, or sickle cell disease.

ASA, American Society of Anesthesiologists; BMI, body mass index; bp, blood pressure; DVT, deep venous thrombosis; EDH, epidural hematoma; ICU, intensive care unit; IQR, interquartile range; ISS, Injury Severity Scale; PAI, platelet aggregation inhibitors; TBI, traumatic brain injury; tSAH, traumatic subarachnoid hemorrhage; VTE, venous thromboembolism.
acid, and extracranial surgery. The median length of hospital stay in patients receiving pVTE prophylaxis was 20 days (interquartile range [IQR], 11–36) versus 7 days (IQR, 3–14) in patients without pVTE prophylaxis. A similar pattern was noted for patients receiving pVTE prophylaxis during ICU stay versus patients receiving no pVTE prophylaxis or after ICU stay. (Table 1) Patients treated in centers using more pVTE prophylaxis were more severely injured (based on the GCS and ISS score) and received more treatments, like invasive blood pressure monitoring, cranial and extracranial surgery, and mechanical prophylaxis (Supplementary File S1).

Overall, DVT incidence rates at the ICU (N=22; 1%) and during the hospital stay (N=25; 2%) were low. Further, recorded clinical PE incidence rates were low at the ICU (N=20; 1%) and during the hospital stay (N=24; 2%). VTE events (either DVT and/or PE) occurred in 56 patients, of whom N=49 (88%) received pVTE prophylaxis and N=7 (13%) did not receive pVTE prophylaxis during the hospital stay.

**Pharmaceutical prophylaxis practices**
Most patients received LMWHs: enoxaparin (N=517; 41%), nadroparin (N=230; 18%), dalteparin (N=227; 18%), tinzaparin (N=48; 4%), and parnaparin (N=4; 0%), whereas unfractionated heparin (N=32; 3%) use was rare. The median duration of pVTE prophylaxis was 11 days (confidence interval [CI], 5–23). The median start of pVTE prophylaxis was 54.5 h after the injury (CI, 15–109; Supplementary File S2).

Overall, between-center differences in application of pVTE prophylaxis were high after case mix and random variation correction: An MOR of 2.69 was found.
There was substantial variation in the application of pVTE prophylaxis between countries in Europe (Fig. 3).

Associations with outcome

At patient level, both the adjusted multi-variate model (odds ratio [OR], 1.4 [1.1–1.7]) as well as the propensity score model (OR, 1.5 [1.1–2.0]) showed better 6-month GOSE scores in patients with pVTE prophylaxis started at some point during the hospital stay (Table 2).

At center level, no major differences in patient population (case mix) between aggressive and non-aggressive centers were found for patient characteristics regarding injury severity (Supplementary File 2). A comparable association between pVTE prophylaxis and outcome was found, but this did not reach significance (OR, 1.2 [0.7–2.1]; Table 2).

Analysis of pVTE prophylaxis in the subgroup analyses at patient level did show associations with improved outcome, although this did not reach statistical significance in all subgroups. Effect estimates for the use of pVTE prophylaxis during ICU stay were similar as well (Table 2).

Survival analyses also showed a beneficial effect of pVTE prophylaxis on survival (p <0.001; Fig. 4). No effect on clinical CT progression was found (OR, 0.9; CI, 0.6–1.2). When analyzing the effect of different drugs for pVTE prophylaxis, we found that they all were associated with improved outcome compared to no pVTE prophylaxis, all with a comparable effect size: enoxaparin (OR, 1.5 [1.2–1.9]); dalteparin (OR, 1.4 [1.0–1.9]); nadroparin (OR, 1.2 [0.9–1.7]); and other (OR, 1.5 [1.2–2.0]).

Discussion

Substantial variation at country and center level was found in the use of pVTE prophylaxis, beyond case-mix differences and random variation. Use of pVTE prophylaxis was associated with improved outcome after 6 months, when administered at the ICU or subsequently at the ward. Overall, this indicates that VTE prophylaxis seems safe and might improve outcomes in critically ill TBI patients. However, given the low incidence of clinically evident VTEs, the pathophysiology explaining this association is not clear from this analysis.

To our knowledge, no previous studies have described between-center variation in pVTE prophylaxis. These variations were observed at both center and country level, and persisted despite correction for random variation and case-mix, suggesting that application of pVTE prophylaxis is driven by hospital policy and local clinical culture. We found a low reported incidence of VTE in patients with TBI in neurotrauma centers in Europe. Although higher incidences of VTE have been reported in previous studies in TBI, others reported similar or even lower percentages compared with our study. The discrepancy between higher incidences in other studies may be partly explained either by a lack of routine lower-limb screening with ultrasound for DVT or clinical under-reporting of DVT in our study. In our study, no conclusion on these outcomes (DVT and PE) could be drawn given that the statistical power was very low.
The association between pVTE prophylaxis and potentially improved functional outcome after 6 months suggests that the benefits of pVTE prophylaxis may outweigh the risks. This result was consistent among all level analyses performed, strengthening the finding of the direction of the effect (improved outcome) and rendering the possibility of a harmful effect less likely. In addition, patients receiving pVTE were more severely injured (based on the GCS and ISS score, number of contusions on CT, and length of stay) compared with patients without pVTE prophylaxis, indicating that in the case of insufficient adjustment, the association between the use of pVTE prophylaxis and improved outcome would be even stronger. Also, no effect of pVTE prophylaxis on CT expansion was found. Previous large studies on the effectiveness of pVTE prophylaxis did not translate to high-level evidence.\textsuperscript{18} At center level, the analyses did not reach significance, but interpretation of these results is difficult given that the statistical power at center level was very low.\textsuperscript{19} Similar associations with outcome after 6 months were found with the use of pVTE prophylaxis during ICU stay. Survival analyses also showed an improvement in survival during the hospital stay. Overall, our results suggest that providing pVTE prophylaxis might improve outcome.

The mechanisms behind possibly improved outcome might be less straightforward than currently thought, given the low incidence of clinical VTE. When taken at face value, the outcome associations found may appear to be less likely caused by a decrease of VTE in patients treated with pVTE prophylaxis (given very low incidence in our study) and may therefore indicate a protective effect of this treatment attributable to mechanisms not yet elucidated. One hypothesis might be that pVTE prophylaxis might reduce

| Table 2. Associations of Pharmaceutical VTE Prophylaxis with 6-Month Outcome |

| Center level | Patient level |
|--------------|--------------|
| IV analyses\textsuperscript{a} | Unadjusted | Adjusted | Propensity score\textsuperscript{b} |
| Inclusion criteria | Prophylaxis during or after ICU stay ICU | N = 2006 | 1.2 [0.7–2.1] | 1.0 [0.8–1.2] | 1.4 [1.1–1.7] | Matches | OR | [CI] |
| Subgroup analyses | Isolated TBI\textsuperscript{c} | N = 900 | 1.0 [0.5–2.1] | 0.9 [0.7–1.1] | 1.2 [0.9–1.6] | 340 | 1.3 [0.9–1.9] |
| Any CT lesion\textsuperscript{d} | N = 1558 | 1.0 [0.5–2.0] | 1.1 [0.9–1.3] | 1.5 [1.2–1.9] | 494 | 1.7 [1.2–2.4] |
| Patients with a long ICU stay (≥72 h) | N = 1315 | 1.1 [0.5–2.2] | 1.1 [0.9–1.4] | 1.6 [1.2–2.2] | 237 | 4.3 [2.3–8.0] |
| Patients with contusions on imaging | N = 984 | 1.2 [0.6–2.5] | 1.2 [0.9–1.5] | 1.3 [1.0–1.7] | 290 | 1.2 [0.8–1.9] |
| Prophylaxis during ICU stay\textsuperscript{e} | ICU | N = 2006 | 1.4 [0.8–2.5] | 0.9 [0.7–1.1] | 1.3 [1.0–1.6] | 706 | 1.2 [0.9–1.5] |

\textsuperscript{a}OR per 100% increase (no use of prophylaxis or use in every patient) corrected for case mix (extended IMPACT model and VTE risk factors), and ordinal GOSE as outcome. The analysis was restricted to centers that contributed >10 patients to the analysis. At patient level, the unadjusted model shows the relation between pharmaceutical prophylaxis use and GOSE without added confounders. The adjusted proportional odds model was corrected for case mix. A propensity-score–matched model was matched on baseline characteristics and VTE risk factors between cases (receiving pharmaceutical DVT prophylaxis) and controls (without pVTE prophylaxis). In this matched data set, the difference outcome was determined between cases and controls.

\textsuperscript{b}Exclusion major extracranial injury.

\textsuperscript{c}Exclusion major extracranial injury.

\textsuperscript{d}Any traumatic intracranial CT abnormality.

\textsuperscript{e}Any traumatic intracranial CT abnormality.

\textsuperscript{f}Center level analyses performed on 48 centers. Center level analyses performed on 48 centers.

\textsuperscript{g}Inclusion criteria: OR [CI] OR [CI] OR [CI] Matches OR [CI].

\textsuperscript{h}Exclusion major extracranial injury.

\textsuperscript{i}Any traumatic intracranial CT abnormality.

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microthrombi in the penumbra of contusional lesions.20–22 The hypothesis was substantiated by a beneficial result of pVTE prophylaxis in the subgroup analyses with patients with contusions. Another hypothesis is that the use of pVTE prophylaxis might improve outcome beyond that expected by the antithrombotic effect, which might be attributable to an anti-inflammatory effect of pVTE prophylaxis and might reduce neuroinflammation. This beneficial anti-inflammatory effect of pVTE prophylaxis is already shown in various mouse models, but needs to be confirmed in future trials.23,24 Others might argue that patients without pVTE prophylaxis would receive mechanical VTE prophylaxis instead. However, this was not confirmed in our results (only around one third of patients without pVTE prophylaxis received mechanical prophylaxis instead).

This study has several strengths and limitations. In the CENTER-TBI study, multiple neurotrauma centers participated from different countries, enabling us to study between-center variation and effectiveness at center level. Several statistical methods were applied. These methods complement each other in their advantages and disadvantages.19 For example, center-level analyses (instrumental variable analyses) are suitable to abolish effects of unmeasured confounding, whereas the power of patient-level analyses is higher, in spite of only being able to adjust for measured confounders. Further, we performed survival analysis to correct for the substantial difference in length of stay between patients with and without pVTE.

This study also has its limitations. CT progression during hospital stay was scored by clinicians subjectively without accounting for a time component. Further routine CT follow-up was not prescribed at specific time points in the protocol. So, it could be that pVTE prophylaxis was administrated after the CT progression occurred. Also, CT progression was not clearly defined (e.g., only progression of cerebral bleeding or other traumatic lesions). The longer length of ICU and hospital stay in patients receiving pVTE prophylaxis compared to the non-pVTE group suggest the possibility of different subpopulations (and a potential higher risk profile in patients receiving pVTE). However, although residual confounding cannot be excluded, the IV analyses and different statistical approaches should account for residual confounding and show similar directions of the effect.

Future studies are needed to elucidate the mechanism behind the beneficial effect of pVTE prophylaxis and determine the best time to initiate prophylaxis. An additional quantitative volumetric analysis of CT progression would be sensitive. In the ideal scenario, an RCT should be considered to confirm our findings, which were obtained in an observational study utilizing comparative effectiveness approaches. However, the extreme heterogeneity of the TBI population in the ICU may render a strict protocol with standardization on when to apply the pVTE prophylaxis challenging.

**Conclusion**

Substantial between-center variation exists in the use of pVTE prophylaxis, whereas pVTE prophylaxis might be associated with improved 6-month functional outcome and lower mortality rates, without CT progression. Therefore, although VTE prophylaxis is likely to be safe, further research should be conducted to confirm and elucidate the associations and should be aimed at a better selection of patients more likely to benefit from this treatment.

**Availability of data and materials**

The used data sets that are analyzed in this study are available after a reasonable request.14
In each recruiting center, ethical approval was given; an online overview is available ([https://www.center-tbi.eu/project/ethical-approval](https://www.center-tbi.eu/project/ethical-approval)). Consent for study participation was obtained according to local legislation from the patient, legal representative, or next of kin, for all patients recruited.\(^{14}\)

**Acknowledgments**
First, the authors thank all patients for participating in the CENTER-TBI study. Second, the authors thank all principal investigators and researchers for collection of ICU data (Collaboration group, Supplementary Reference S3).

**Authors’ Contributions**
J.H. analyzed the data. The analyses were checked and results were reproduced by D.P. The data were interpreted by J.H., D.P., E.W., M.J., and H.L. J.H. drafted the manuscript, including all tables and figures. J.H., E.W., M.J., D.P., and H.L. were involved in regular meetings on the manuscript. H.L. supervised the study. All authors reviewed the manuscript multiple times before submission and approved the final version of the manuscript.

**Funding Information**
This research is funded by the European Commission 7th Framework program (602150). The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

**Author Disclosure Statement**
A.I.R.M. declares consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. D.K.M. reports grants from the UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; and personal fees from Neurotrauma Sciences, Lantmaanen AB, Prescura, and Pfizer, outside of the submitted work. E.S. reports personal fees from Springer, during the conduct of the study. All other authors declare no competing interests.

**Supplementary Material**
Supplementary File S1 (table)
Supplementary File S2 (figure)
Supplementary File S3 (collaborator’s list)

**References**
1. Abdel-Aziz, H., Dunham, C.M., Malik, R.J., and Hileman, B.M. (2015). Timing for deep vein thrombosis chemoprophylaxis in traumatic brain injury: an evidence-based review. Crit. Care 19, 96.
2. Reiff, D.A., Haricharan, R.N., Bullington, N.M., Griffin, R.L., McGwin, G., Jr., and Rue, L.W. III. (2009). Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. J Trauma 66, 1436–1440.
3. Ekeh, A.P., Dominguez, K.M., Markert, R.J., and McCarthy, M.C. (2010). Incidence and risk factors for deep venous thrombosis after moderate and severe brain injury. J Trauma 68, 912–915.
4. Carney, N., Totten, A.M., O’Reilly, C., Ullman, J.S., Hawryluk, G.W., Bell, M.J., Bradton, S.L., Chesnut, R., Harris, O.A., Kissoon, N., Rubiano, A.M., Shutter, L., Tasker, R.C., Vavilala, M.S., Wilberger, J., Wright, D.W., and Ghajar, J. (2017). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 80, 6–15.
5. Phelan, H.A., Wolf, S.E., Norwood, S.H., Aldy, K., Brakenridge, S.C., Eastman, A.L., Madden, C.J., Nakonezny, P.A., Yang, L., Chason, D.P., Arbique, G.M., Berne, J., and Minej, P.J. (2012). A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: the Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study. J. Trauma Acute Care Surg. 73, 1434–1441.
6. Skrifvars, M.B., Bailey, M., Presnell, J., French, C., Nichol, A., Little, L., Duranteau, J., Huet, O., Haddad, S., Arabic, Y., McArthur, C., Cooper, D.J., and Bellomo, R. EPO-TBI investigators and the ANZICS Clinical Trials Group. (2017). Venous thromboembolic events in critically ill traumatic brain injury patients. Intensive Care Med. 43, 419–428.
7. CRASH-3 trial collaborators. (2019). Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 394, 1713–1723.
8. Levy, A.S., Salototto, K., Bar-Or, R., Offner, P., Mains, C., Sullivan, M., and Bar-Or, D. (2010). Pharmacologic thromboprophylaxis is a risk factor for hemorrhage progression in a subset of patients with traumatic brain injury. J Trauma 68, 886–894.
9. Kwiatz, M.E., Patel, M.S., Ross, S.E., Lachant, M.T., MacNiew, H.G., Ochsner, M.G., Norwood, S.H., Speier, L., Kozar, R., Gerber, J.A., Rowell, S., Krishnakumar, S., Livingston, D.H., Manis, G., and Haan, J.M. (2012). Is low-molecular-weight heparin safe for venous thromboembolism prophylaxis in patients with traumatic brain injury? A Western Trauma Association multicenter study. J Trauma Acute Care Surg. 73, 625–628.
10. Scudder, T., Brasel, K., Webb, T., Codner, P., Somberg, L., Weigelt, J., Herrmann, D., and Peppard, W. (2011). Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. J. Am. Coll. Surg. 213, 148–153; discussion, 153–154.
11. Minshall, C.T., Eriksson, E.A., Leon, S.M., Doben, A.R., McKinzie, B.P., and Falhry, S.M. (2011). Safety and efficacy of heparin or enoxaparin prophylaxis in blunt trauma patients with a head abbreviated injury severity score \(>2\). J. Trauma 71, 396–399; discussion, 399–400.
12. Maas, A.I., Menon, D.K., Steyerberg, E.W., Citerio, G., Lecky, F., Manley, G.T., Hill, S., Legrand, V., and Sorgner, A.; CENTER-TBI Participants and Investigators. (2015). Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 76, 67–80.
13. Steyerberg, E.W., Wiegens, E., Sevalt, C., Buki, A., Citerio, G., De Keyser, V., Ercule, A., Kunzmann, K., Lanyon, L., Lecky, F., Lingsma, H., Manley, G., Nelson, D., Peul, W., Stocchetti, N., von Steinbuchel, N., Vande Vyvere, T., Verheyden, J., Wilson, L., Maas, A.I.R., and Menon, D.K.; CENTER-TBI Participants and Investigators. (2019). Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. Lancet Neurol. 18, 923–934.
14. CENTER-TBI. (2021). Ethical approval. www.center-tbi.eu/project/ethical-approval (Last accessed March 2, 2020).
15. Merlo, J., Chais, B., Ohlsson, H., Beckman, A., Johnell, K., Hjerpe, P., Rastam, L., and Larsson, K. (2006). A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J. Epidemiol. Community Health 60, 290–297.
16. Van Buuren, S., and Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. J. Stat. Softw. 45, 1–67.

17. Nichol, A., French, C., Little, L., Haddad, S., Presneill, J., Arabi, Y., Bailey, M., Cooper, D.J., Duranteau, J., Huet, O., Mak, A., McArthur, C., Pertilla, V., Skrifvars, M., Vallance, S., Varma, D., Wills, J., and Bellomo, R.; EPO-TBI Investigators; ANZICS Clinical Trials Group. (2015). Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 386, 2499–2506.

18. Chelladurai, Y., Stevens, K.A., Haut, E.R., Brotman, D.J., Sharma, R., Shermock, K.M., Kebede, S., Singh, S., and Segal, J.B. (2013). Venous thromboembolism prophylaxis in patients with traumatic brain injury: a systematic review. F1000Res. 2, 132.

19. Cnossen, M.C., van Essen, T.A., Ceyisakar, I.E., Polinder, S., Andriessen, T.M., van der Naalt, J., Haitsma, I., Horn, J., Franschman, G., Vos, P.E., Peul, W.C., Menon, D.K., Maas, A.L., Steyerberg, E.W., and Lingsma, H.F. (2018). Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. Clin. Epidemiol. 10, 841–852.

20. Schwarzmaier, S.M., Kim, S.W., Trabold, R., and Plesnila, N. (2010). Temporal profile of thrombogenesis in the cerebral microcirculation after traumatic brain injury in mice. J. Neurotrauma 27, 121–130.

21. Zhang, J., Zhang, F., and Dong, J.F. (2018). Coagulopathy induced by traumatic brain injury: systemic manifestation of a localized injury. Blood 131, 2001–2006.

22. Fletcher-Sandersjoo, A., Thelin, E.P., Maegele, M., Svensson, M., and Bellander, B.M. (2021). Time course of hemostatic disruptions after traumatic brain injury: a systematic review of the literature. Neurocrit. Care. 34, 635–656.

23. Simon, D.W., McGeachy, M.J., Bayir, H., Clark, R.S., Loane, D.J., and Kochanek, P.M. (2017). The far-reaching scope of neuroinflammation after traumatic brain injury. Nat. Rev. Neurol. 13, 171–191.

24. Smeeth, L., Cook, C., Thomas, S., Hall, A.J., Hubbard, R., and Vallance, P. (2006). Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 367, 1075–1079.

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**Abbreviations Used**

ASA = American Society of Anesthesiologists
CI = confidence interval
CT = computed tomography
DVT = deep venous thrombosis
ED = emergency department
EDH = epidural hematoma
GCS = Glasgow Coma Scale
GOSE = Glasgow Outcome Scale-Extended
ICU = intensive care unit
IQR = interquartile range
ISS = Injury Severity Score
IV = instrumental variable
LMWH = low-molecular-weight heparin
OR = odds ratio
PE = pulmonary embolism
pVTE = pharmaceutical VTE
RCTs = randomized controlled trials
TBI = traumatic brain injury
tSAH = traumatic subarachnoid hemorrhage
VTE = venous thromboembolism