# Venous thromboembolism prophylaxis and related outcomes in patients with traumatic brain injury and prolonged intensive care unit stay

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**ABSTRACT**

**Objective:** Traumatic brain injury (TBI) patients with prolonged intensive care unit (ICU) stay are at risk of secondary intracranial haemorrhage (ICH) and venous thromboembolism (VTE). We aimed to study VTE prophylaxis, secondary ICH, and VTE prevalence and outcomes in this population.

**Design:** Retrospective observational study.

**Setting:** Level 1 trauma centre ICU.

**Patients:** One hundred TBI patients receiving prolonged ICU treatment (≥ 7 days).

**Interventions:** We collected data from medical records, pathology and radiology systems, and hospital and ICU admission databases. We analysed patient characteristics, interventions, episodes and types of secondary ICH and VTE, and timing and dosage of VTE prophylaxis.

**Results:** Data from the 100 patients in our study showed that early use of compression stockings and pneumatic calf compression was common (75% and 91% in the first 3 days, respectively). VTE chemoprophylaxis, however, was only used in 14% of patients by Day 3 and > 50% by Day 10. We observed VTE in 12 patients (10 as pulmonary embolism), essentially all after Day 6. Radiologically confirmed secondary ICH occurred in 43% of patients despite normal coagulation. However, 72% of ICH events (42/58) were radiologically mild, and the median time of onset of ICH was Day 1, when only 3% of patients were on chemical prophylaxis. Moreover, 82% of secondary ICH events (48/58) occurred in the first 3 days, with no severe ICH thereafter.

**Conclusions:** In TBI patients receiving prolonged ICU treatment, early chemical VTE prophylaxis was uncommon. Early secondary ICH was common and mostly radiologically mild, whereas later secondary ICH was essentially absent. In contrast, early VTE was essentially absent, whereas later VTE was relatively common. Earlier chemical VTE prophylaxis and/or ultrasound screening in this population appears logical.

Crit Care Resusc 2021; 23 (4): 364-73

The incidence of traumatic brain injury (TBI) in Australia is about 100 per 100 000 people, with 180-day mortality rates of 30–35% and vast subsequent social and medical costs, both financial and human.[1-3] Patients with TBI are at increased risk of both secondary intracranial haemorrhage (ICH) and venous thromboembolism (VTE),[4] with the prevalence for TBI patients being higher than that for other hospitalised patients.[5]

In TBI patients, chemical VTE prophylaxis appears effective in reducing VTE rates, and its use has been associated with low or no incidence of ICH progression.[6-14] However, despite multiple observational studies showing that chemical prophylaxis may be safe and effective,[6,10,11,13,14] many clinicians are reluctant to use it in the first week. This is largely due to lack of randomised controlled trials and/or an accepted standard of care.[15] Moreover, to our knowledge, current use of VTE prophylaxis in TBI patients experiencing a prolonged ICU stay (> 7 days) has not previously been described. This is despite such patients being likely to have a particularly high risk of VTE as they remain essentially immobilised in an ICU for a week or longer. Lack of data regarding this group of TBI patients makes it difficult to understand their usual care, estimate the prevalence of ICH and VTE, and design interventional studies of such very high risk populations.

Accordingly, we conducted a retrospective study to investigate the types of VTE prophylaxis used, including chemical prophylaxis, and the timing of its initiation in patients with TBI who received prolonged ICU treatment (≥ 7 days) at a major Level 1 trauma centre in Melbourne, Australia. In addition, we aimed to define the prevalence and timing of secondary ICH and VTE in the setting of such practice. We hypothesised that secondary ICH would be common but mostly occur early, that early use of chemical prophylaxis (first week) would be relatively uncommon, and that VTE would be common but mostly occur late (after Day 7).

## Methods

We retrospectively investigated current clinical practice pertaining to VTE prophylaxis in TBI patients who were admitted to the ICU of a major trauma centre and who remained in the ICU for ≥ 7 days. The Human Research Ethics Committee of the Royal Melbourne Hospital approved the conduct of this study. We selected 100 trauma centre patients who had an admission code from 601.01 to 601.08 in the Australian and New Zealand Intensive Care Society (ANZICS) ICU database using a random number generator. Key inclusion criteria were: TBI with admission to ICU between 1 January 2015 and 31 December 2019; age > 18 years; and treatment with mechanical ventilation. We excluded patients if they had an ICU admission of < 7 days or if they were pregnant. We collected clinical data from chart review of electronic medical records, clinical information systems, and pathology and radiology systems, and we obtained administrative data from the Victorian Admitted Episodes Dataset and ANZICS database.

### Demographic and clinical data

The data we collected included: patient characteristics (eg, date of birth, age, sex, weight); diagnosis; Glasgow Coma Scale (GCS) score and Acute Physiology and Chronic Health Evaluation (APACHE) III score on admission; ICU and hospital length of stay; survival until ICU and hospital discharge; invasive ventilation and renal replacement therapy duration; insertion of an intracranial pressure (ICP) monitor and/or external ventricular drain (EVD); imaging results including computed tomography (CT) scan of the head, CT pulmonary angiogram and lower limb ultrasound; deep venous and pulmonary thromboembolic events during entire hospital admission; radiologically diagnosed secondary ICH during ICU admission; mechanical and chemical VTE prophylaxis; surgical procedures during ICU admission; and platelet levels, international normalised ratio, and activated plasma thromboplastin time during ICU admission. All investigations for possible VTE occurred on the basis of clinical suspicion and were dictated by protocol.

### Identification of intracranial haemorrhage

We defined secondary ICH according to the presence of a radiological report describing a new area of intracranial bleeding on a CT scan of the head, using any of the following terms: new bleeding, new haemorrhage, extension of haemorrhage, secondary bleeding, secondary haemorrhage, increase in size, increase in depth, interval increase, increase compared with previous, further bleeding, further haemorrhage, additional bleeding, and additional haemorrhage. We categorised a secondary ICH as mild, moderate or severe according to its description in the radiological report. For mild ICH, we used adjectives like small, mild, negligible, minute and limited. For moderate ICH, we used adjectives like moderate, medium-sized and mid-sized. For severe ICH, we used adjectives like severe, marked, substantial, large, significant and noticeable.

### Data on venous thromboembolism

We collected data pertaining to VTE prophylaxis, haematological findings and procedures conducted on Days 1–10 of ICU admission and then every third day until Day 28 of ICU admission. We counted Day 1 as the day of ICU admission. We did not include readmissions to an ICU, we only included ICH events if they occurred during the ICU admission, and we considered thromboembolic events across the entirety of the hospital admission (ie, from admission to discharge from hospital).

### Statistical analysis

We classified patients according to the development of VTE or the presence of new radiologically described ICH during follow-up. We present continuous data as median (interquartile range), which we compared with between-group analysis using the Wilcoxon rank-sum test. We present categorical data as number (percentage), which we compared with between-group analysis using the Fisher exact test. We present the percentages of patients receiving VTE prophylaxis over the first 28 days of follow-up as Kaplan–Meier plots and compared groups with the log-rank test. Hypothesis testing was two sided with a significance level of 0.05. We performed analyses using R v4.0.2 (R Core Team).

## Results

We screened 659 TBI patients admitted to the ICU during the study period, of whom 451 met exclusion criteria. This left a cohort of 208 eligible patients, from which we randomly selected 100 patients for analysis.

### Baseline characteristics and clinical course

The baseline characteristics of the 100 study patients are summarised in Table 1. Patients were mostly men, their median age was 51.9 years, and their median APACHE III score was 61. Their median length of ICU stay was 11 days and median duration of endotracheal intubation was 9 days. The all-cause in-hospital mortality rate was 15%, and 60% of deaths (9/15) occurred during the first ICU admission. Median ICU and hospital length of stay were longer among patients who developed VTE. As shown in Table 1, patients who developed VTE had a higher median APACHE III score and a lower median GCS score. Patients with at least one episode of ICH had a lower median GCS score, were more likely to die during their ICU or hospital admission, and had a longer median duration of ventilation (Table 2).

**Table 1. Baseline characteristics and clinical outcomes of study patients according to the development of VTE***

| | VTE (*n* = 12) | No VTE (*n* = 88) | *P* |
|---|---|---|---|
| Age, years | 43.8 (25.9–59.2) | 52.3 (25.5–68.3) | 0.596 |
| Men | 9 (75%) | 74 (84%) | 0.424 |
| Weight, kg | 81.5 (74.3–94.6) | 81.0 (70.0–95.0) | 0.599 |
| APACHE III score at admission | 76.5 (63.0–86.2) | 57.5 (43.8–73.0) | 0.026 |
| GCS score at admission | 4.0 (3.0–8.2) | 8.5 (6.0–13.0) | 0.017 |
| Clinical outcomes | | | |
| Reintubation | 1 (8%) | 4 (5%) | 0.480 |
| Duration of ventilation, days† | 11.0 (8.8–17.5) | 8.0 (6.0–12.0) | 0.089 |
| ICU length of stay, days | 16.5 (11.9–22.2) | 10.1 (8.0–13.4) | 0.008 |
| Hospital length of stay, days | 51.3 (29.2–71.7) | 21.4 (14.4–32.4) | < 0.001 |
| ICU mortality | 1 (8%) | 8 (9%) | 0.999 |
| Hospital mortality | 1 (8%) | 13 (15%) | 0.999 |

APACHE = Acute Physiology and Chronic Health Evaluation. GCS = Glasgow Coma Scale. ICU = intensive care unit. VTE = venous thromboembolism. * Data are median (interquartile range [quartile 25% – quartile 75%]) or number (%). † Including additional ventilation time for reintubated patients.

**Table 2. Baseline characteristics and clinical outcomes according to the development of secondary intracranial bleeding***

| | Intracranial bleeding (*n* = 43) | *No intracranial bleeding (n = 57)* | *P* |
|---|---|---|---|
| Age, years | 59.6 (29.1–73.4) | 46.7 (25.3–62.6) | 0.067 |
| Men | 33 (77%) | 50 (88%) | 0.183 |
| Weight, kg | 80.0 (70.0–89.9) | 81.2 (72.7–95.1) | 0.340 |
| APACHE III score at admission | 64.0 (48.5–77.0) | 57.0 (43.0–74.0) | 0.382 |
| GCS score at admission | 8.0 (5.0–10.0) | 9.0 (5.0–13.0) | 0.037 |
| Clinical outcomes | | | |
| Reintubation | 3 (7%) | 2 (4%) | 0.649 |
| Duration of ventilation, days† | 10.0 (7.0–15.0) | 8.0 (5.0–11.0) | 0.011 |
| ICU length of stay, days | 11.9 (8.5–15.0) | 10.4 (7.6–14.0) | 0.475 |
| Hospital length of stay, days | 22.9 (17.9–39.5) | 22.1 (14.5–32.4) | 0.301 |
| ICU mortality | 7 (16%) | 2 (4%) | 0.036 |
| Hospital mortality | 11 (26%) | 3 (5%) | 0.007 |

APACHE = Acute Physiology and Chronic Health Evaluation. GCS = Glasgow coma scale. ICU = intensive care unit. * Data are median (interquartile range [quartile 25% – quartile 75%]) or number (%).
† Including additional ventilation time for reintubated patients.

Median international normalised ratio and activated plasma thromboplastin time values were within their respective reference intervals between Day 1 and Day 10 of ICU admission with no significant changes over time. Median platelet levels remained above 150 × $10^9$/L from Day 1 to Day 8 but increased significantly compared with baseline after Day 8. The overall use of investigations (head magnetic resonance imaging, head CT scan, CT pulmonary angiogram, lower limb ultrasound) and interventions (continuous renal replacement therapy, inferior vena cava [IVC] filter placement, insertion of ICP monitor or EVD device) are presented in the Online Appendix (Table e1).

Overall, 62% of patients had at least one surgical procedure during their ICU admission. The types of surgical procedures and their timings are shown in the Online Appendix (Table e2). Orthopaedic surgery was the most common single type of surgery, while neurosurgery was the least common (Online Appendix, Figure e1). Most neurosurgical procedures occurred in the first 2 days of ICU admission, and only five neurosurgical procedures occurred after Day 3. Orthopaedic surgical procedures (*n* = 51) were also performed early, confirming the presence of multitrauma in most patients, with 51% (26/51) completed by Day 3 and 82% (42/51) by Day 5.

Overall, 95% of patients received at least one head CT scan during their ICU admission, and there was a median of two head CT scans per patient. Most such scans were performed early — 92.6% (246/266) were performed in the first 3 days and 98.9% (263/266) were performed by Day 7. In addition, 28% of patients had at least one CTPA, and the median time to first CTPA was 9.8 days after ICU admission. Finally, only 15% of patients had at least one lower limb Doppler ultrasound,

and median time to first such scan was 9.5 days after ICU admission. Seven patients had both CTPA and Doppler lower limb ultrasound during their hospital admission.

Five patients received an IVC filter during their ICU admission (one on Day 46 and only three patients in the first 7 days); median time of IVC filter insertion was Day 6 of ICU admission. The data on IVC filters, chemical prophylaxis, intracranial bleeding and VTE on each day in the first 2 weeks after ICU admission are shown in Figure 1. Patients who developed VTE were more likely to receive an IVC filter compared with those who were not diagnosed with VTE during their admission (25% [3/12] *v* 2.3% [2/88]; $P = 0.01$). The median time of IVC filter insertion in the subset of three patients who developed a VTE was Day 16 of ICU admission. Only two patients had an IVC filter inserted prophylactically.

### Prophylaxis for deep vein thrombosis

Early mechanical prophylaxis against deep vein thrombosis, such as use of calf compressors and thromboembolic deterrent (TED) stockings, was common (Table 3). Within the first 3 days of ICU admission, 75% of all patients had TED stockings fitted and 91% had calf compressors fitted, and the median time until first use of either was 2 days. Within the 7 days of ICU admission, 95% of all patients had calf compressors fitted and 89% had TED stockings fitted, and the median duration of use was 6 days (interquartile range, 5–7 days) for calf compressors and 5 days (interquartile range, 2–7 days) for TED stockings. In contrast, only 14% of patients commenced chemical prophylaxis by Day 3 of ICU admission, with a median time until commencement of 6.5 days. The use of calf compression, TED stockings and chemical prophylaxis during the first 2 weeks in patients who did and did not develop VTE is shown in Figure 2.

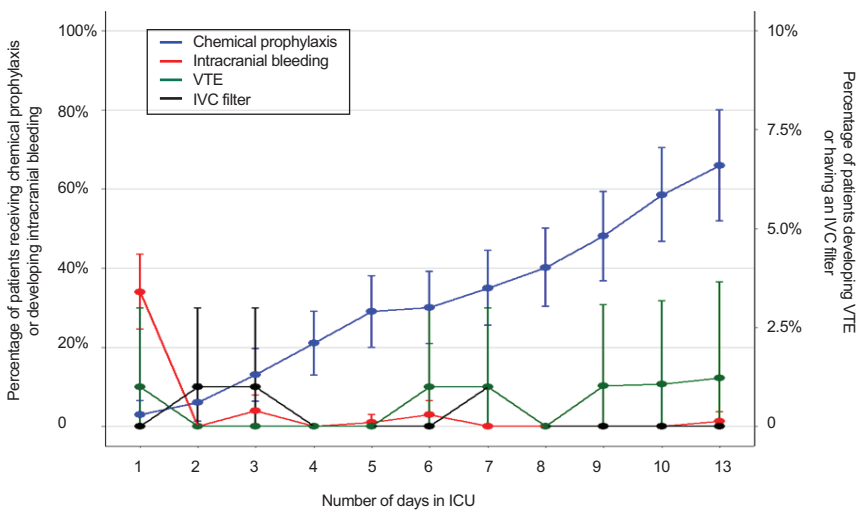
It was not until Day 25 that 100% of patients still in ICU were receiving chemical VTE prophylaxis. The most common type of chemical DVT prophylaxis was subcutaneous enoxaparin at a dose of 40 mg daily, consistent with the unit VTE prophylaxis guidelines. Five patients received prophylactic subcutaneous unfractionated heparin at a dose of 5000 IU twice daily, and two received intravenous heparin (one of whom was concurrently receiving post-filter protamine for continuous renal replacement therapy). Finally, three patients received bivalirudin because of suspected heparin-induced thrombocytopenia.

APACHE III scores and age were not significantly associated with use of mechanical prophylaxis (Online Appendix, Figure e2). However, for chemical prophylaxis, APACHE III scores showed an association; 50% of patients with a score below the median (< 61) were on chemical prophylaxis by Day 4 compared with less than 20% of patients with a score > 61 (Online Appendix, Figure e3). In contrast, age was not significantly associated with chemical prophylaxis (Online Appendix, Figure e3).

### Intracranial haemorrhage and venous thromboembolism

A radiologically diagnosed secondary ICH after ICU admission occurred in 43% of patients, for a total of 58 ICH events. Of these, 72% (42/58) were radiologically categorised as mild and 12% (7/58) as severe. Median time of secondary ICH onset was Day 1 when only 3% of patients were on chemical VTE prophylaxis. Overall, 81% (47/58) of all secondary ICH events occurred by Day 3. Seven secondary ICH episodes were on the day of or day before a neurosurgical procedure. Moreover, seven patients had a secondary ICH on the day of or day before insertion of an ICP monitor or EVD device.

**Figure 1. Percentages of patients who developed intracranial bleeding or VTE, received VTE chemoprophylaxis and had an IVC filter in the first 2 weeks after ICU admission**




ICU = intensive care unit. IVC = inferior vena cava. VTE = venous thromboembolism.

**Table 3. Use of VTE prophylaxis according to the development of VTE***

| | VTE (*n* = 12) | No VTE (*n* = 88) | *P* |
|---|---|---|---|
| Time until first use of TED stockings, days | 2.0 (1.0–3.5) | 2.0 (1.0–3.0) | 0.519 |
| Time until first use of calf compression, days | 2.0 (1.0–2.0) | 2.0 (1.0–2.0) | 0.581 |
| Time until first use of chemical prophylaxis, days | 8.0 (6.5–13.0) | 6.0 (4.0–9.0) | 0.067 |
| First 3 days | | | |
| TED stockings used | 8 (67%) | 67 (76%) | 0.488 |
| Duration of TED stocking use, days | 1.5 (0.0–3.0) | 2.0 (1.0–3.0) | 0.652 |
| Calf compression used | 10 (83%) | 81 (92%) | 0.294 |
| Duration of calf compression, days | 2.0 (1.8–3.0) | 2.0 (1.8–3.0) | 0.677 |
| Chemical prophylaxis used | 1 (8%) | 13 (15%) | 0.999 |
| Duration of chemical prophylaxis, days | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.585 |
| First 5 days | | | |
| TED stockings used | 10 (83%) | 75 (85%) | 0.999 |
| Duration of TED stocking use, days | 3.5 (1.8–5.0) | 4.0 (2.0–5.0) | 0.999 |
| Calf compression used | 12 (100%) | 82 (93%) | 0.999 |
| Duration of calf compression, days | 4.0 (2.8–5.0) | 4.0 (3.0–5.0) | 0.747 |
| Chemical prophylaxis used | 2 (17%) | 29 (33%) | 0.333 |
| Duration of chemical prophylaxis, days | 0.0 (0.0–0.0) | 0.0 (0.0–1.0) | 0.273 |
| First 7 days | | | |
| TED stockings used | 11 (92%) | 78 (89%) | 0.999 |
| Duration of TED stocking use, days | 5.0 (2.8–7.0) | 5.5 (2.0–7.0) | 0.987 |
| Calf compression used | 12 (100%) | 83 (94%) | 0.999 |
| Duration of calf compression, days | 6.0 (4.8–7.0) | 6.0 (5.0–7.0) | 0.826 |
| Chemical prophylaxis used | 4 (33%) | 35 (40%) | 0.761 |
| Duration of chemical prophylaxis, days | 0.0 (0.0–1.2) | 0.0 (0.0–3.0) | 0.472 |

TED = thromboembolic deterrent. VTE = venous thromboembolism. * Data are median (interquartile range [quartile 25% – quartile 75%]) or number (%).

Patients who did not develop ICH were more likely to have started chemical prophylaxis in the first 7 days of ICU admission compared with those who developed a secondary ICH (56% [32/57] *v* 16% [7/43]; $P < 0.001$) (Figure 3). Chemical prophylaxis use increased over time, but secondary ICH rates did not. Insertion of an ICP monitor or EVD device was associated with later administration and decreased use of chemical VTE prophylaxis (Online Appendix, Figure e4).

We observed VTE rates of 8% (8/100 during ICU admission and 12% (12/100) across the entire duration of hospital admission. Most of these events (83% [10/12]) were pulmonary embolism (PE). Six patients developed a PE during their ICU admission, and a further four patients after discharge to the ward. Two patients developed deep vein thrombosis during their ICU admission, and one during their ward admission. No patient died from PE.

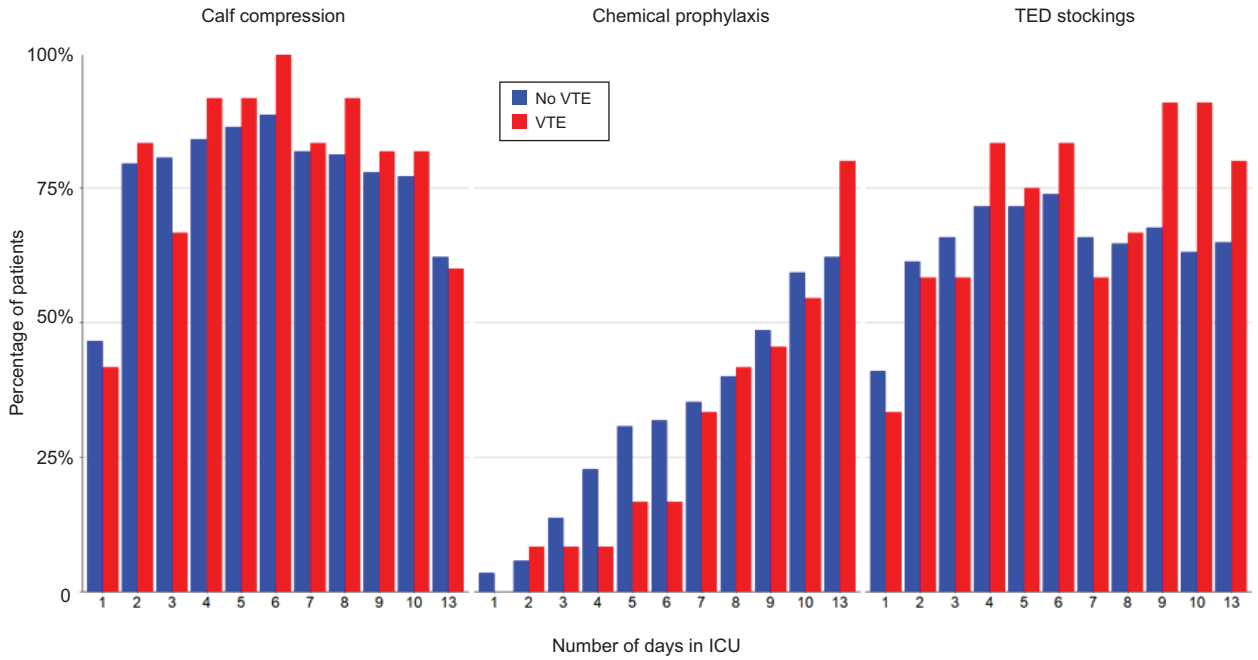
As shown in the Online Appendix (Figure e5), the rate of VTE increased over time from Day 6, whereas the rate of ICH was essentially flat by that time, while chemical prophylaxis was only being administered to a minority of patients. As shown in Figure 4, there were no radiologically diagnosed episodes of new ICH in patients with an ICP monitor or EVD after Day 6. In addition, even after removal of such devices, only half of these patients had started treatment with chemical VTE prophylaxis. Patients who developed VTE tended to start chemical prophylaxis later than those who did not (median time of commencement, ICU Day 8 *v* ICU Day 6; $P = 0.067$).

## Discussion

### Key findings

We studied the use of VTE prophylaxis and the prevalence of ICH and VTE in patients with severe TBI who received prolonged ICU treatment in an Australian Level 1 trauma centre. We found near universal early use of mechanical VTE prophylaxis, but delayed initiation of chemical prophylaxis, particularly in patients with a high APACHE III score and/or ICP monitor or EVD device. Overall, about one in eight patients developed clinically suspected and radiologically confirmed VTE (mostly PE), and almost one in two patients had at least one episode of radiologically diagnosed new ICH. However, essentially all radiologically documented ICH

**Figure 2. Percentages of patients receiving three types of VTE prophylaxis in the first 2 weeks after ICU admission, split according to the subsequent development of VTE***




ICU = intensive care unit. TED = thromboembolic deterrent. VTE = venous thromboembolism. * The uptake of calf compression and TED stocking was rapid in both groups; however, the uptake of chemical prophylaxis was slow and only reached a value > 50% by Day 10, with greater early uptake in patients who subsequently did not develop VTE.

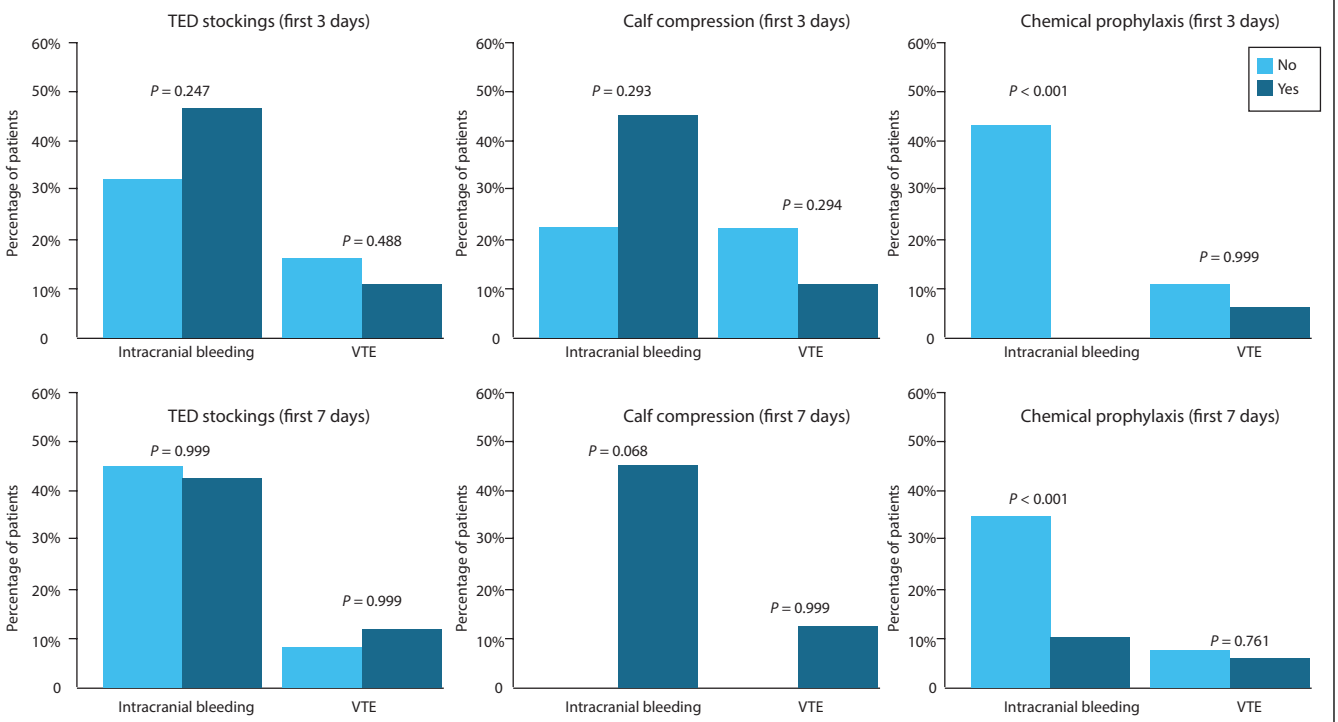
episodes occurred in the first 2 days of ICU admission and most were mild, while essentially all clinically suspected and radiologically confirmed VTE episodes occurred after Day 6.

### Relationship to previous studies

Several observational studies have examined the practice of VTE prophylaxis in TBI patients.[16-18] The most extensive assessment, however, was undertaken as part of the Erythropoietin in Traumatic Brain Injury (EPO-TBI) trial, which included protocol-based twice weekly lower limb ultrasound screening.[19] The EPO-TBI study, conducted between 2010 and 2015, assessed clinical practice in more than 600 patients as part of a multicentre international, double-blind randomised controlled trial. It found a VTE rate of 19.7% compared with the 12% rate recorded in our study. However, this difference is likely related to the twice weekly lower limb ultrasound screening protocol in EPO-TBI, which identified many clinically silent VTE events. These events were predominantly lower limb VTE (81%), while the opposite was true in our cohort. This difference is also likely explained by the EPO-TBI screening protocol. Aligned with our observations, however, the EPO-TBI investigators found early and widespread use of mechanical prophylaxis (91% of patients on Day 1, increasing to 98% of patients by Day 7). In addition, they also found that chemical prophylaxis was delayed and less frequently used than mechanical prophylaxis, with only 57% of patients receiving it by Day 7. This compares to 39% in our cohort. Of relevance to our study, the EPO-TBI investigators also found that, even after adjustment for the severity of TBI, patients treated in Australia and New Zealand were started on chemoprophylaxis significantly later than patients treated in trial centres in other countries. Moreover, patients treated in Australia and New Zealand had twice the odds ratio of developing an episode of VTE compared with patients treated in other countries. The reasons for the comparative reluctance of clinicians in Australia and New Zealand to initiate VTE chemoprophylaxis early are unknown.

The EPO-TBI study did not include North American centres. The most extensive study of VTE prophylaxis in TBI patients from North America is a retrospective single centre study of 812 patients admitted to a Level 1 trauma centre between 2006 and 2008.[13] In this observational study, 49.5% of patients received chemical prophylaxis, and chemical prophylaxis was associated with a reduced

**Figure 3. Percentages of patients who had intracranial bleeding and VTE who were being treated with TED stockings, calf compression and chemical prophylaxis in the first 3 days and first 7 days after ICU admission**




ICU = intensive care unit. TED = thromboembolic deterrent. VTE = venous thromboembolism.

incidence of VTE compared with mechanical prophylaxis or no prophylaxis at all. In addition, chemical prophylaxis was not associated with progression or recurrence of ICH.

In our study, the mortality rate for patients who experienced VTE was low and no patient died from VTE. In contrast, the mortality rate for patients with secondary ICH was high. These differences likely reflect the bias created by selection for investigation, the late occurrence of VTE (which would require survival until the time of investigation), and the younger age of VTE patients compared with ICH patients.

However, no previous studies have been designed to focus on, or provided specific data for, severe TBI patients with a prolonged ICU stay. This makes direct comparisons between our findings and those of previous studies difficult owing to potential effects of selection bias.

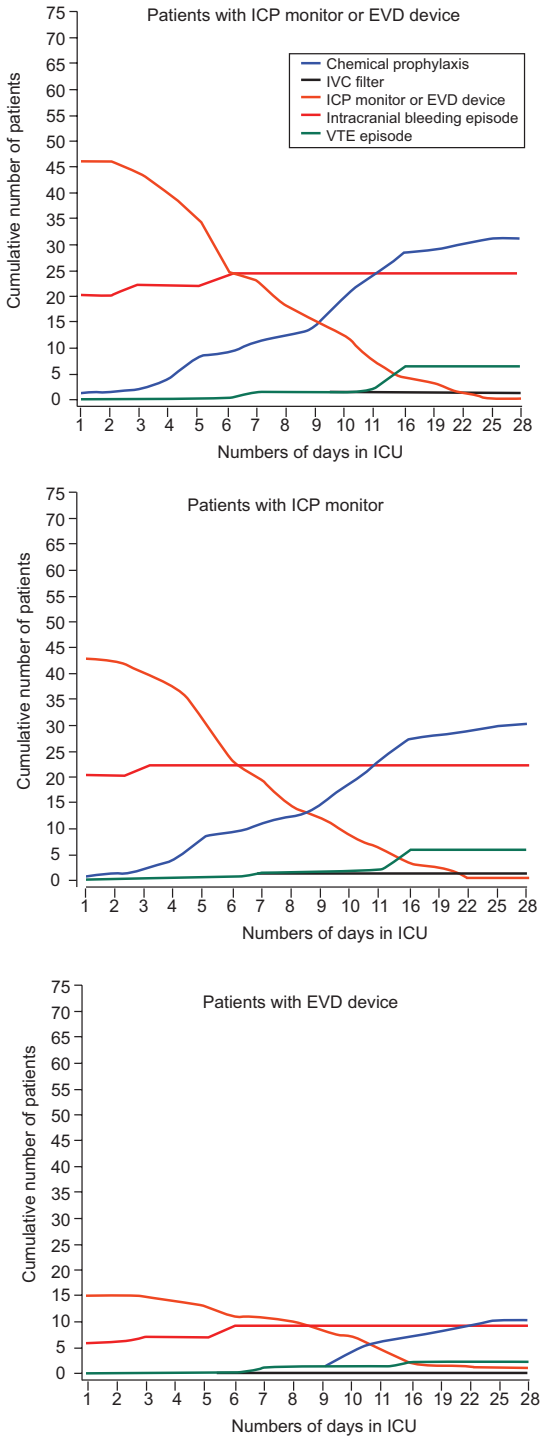
### Study implications

Our findings imply that TBI patients with a prolonged ICU stay often develop new radiologically diagnosed ICH following admission to ICU. However, they do so in the first 2–3 days, with most such episodes being limited or even negligible in terms of radiological size. Our findings also imply that, while early use of mechanical VTE prophylaxis is almost ubiquitous, initiation of chemical prophylaxis is delayed, particularly in patients with greater injury severity, and those who have had an ICP monitor or EVD device inserted. Essentially all radiological ICH events appeared to occur in the first 2 days and most major surgery appeared to have been completed by Day 3, with half of invasive intracranial devices removed by Day 6. In contrast, essentially all VTE episodes appeared to occur after Day 6. Thus, our findings suggest that lower limb ultrasound surveillance and/or intervention with chemoprophylaxis after Day 3 are logical.

### Study strengths and limitations

Our study has several strengths. To our knowledge, it is the only detailed study of VTE prophylaxis in the unique population of TBI patients with extended stay in ICU. Methodologically, numerous parameters were collected across multiple days. This degree of granularity is unprecedented and allowed for detailed exploration of the temporal relationships between risk factors, interventions and outcomes. Our study also provided a baseline overview of current practice at a major trauma centre, which serves as a foundation for the development of future

**Figure 4. Cumulative numbers of patients who received interventions, had VTE episodes and had intracranial bleeding episodes according to the presence of ICP monitor and EVD device, assessed until 4 weeks after ICU admission**




EVD = external ventricular drain. ICP = intracranial pressure. ICU = intensive care unit. IVC = inferior vena cava. VTE = venous thromboembolism.

chemoprophylaxis protocols and interventional studies. Finally, the study cohort was randomly selected and data collectors were blinded to outcomes, thus minimising selection or ascertainment bias.

We acknowledge several limitations. Despite the size of the cohort, this is a single centre study. This raises concerns about the external validity of the study findings. However, the study centre is one of only two Level 1 trauma centres in Victoria, Australia — a state with a population of more than 6.5 million. As a retrospective observational study, our investigation could not identify causal factors underlying VTE and ICH. Nonetheless, it identified factors to be investigated in prospective studies and provided data on important clinical risk factors. Our selection of patients who remained in the ICU for more than 7 days led to the exclusion of almost 70% of patients in the database, mostly because of either early death or short duration of intubation. We cannot comment on their characteristics and acknowledge the potential impact of selection bias on our data regarding VTE. In addition, clinicians faced with patients in the first few days in ICU may not be able to judge whether a patient will remain in ICU for longer than a week. However, we provide descriptive data for clinicians to help them identify the kinds of patients studied. Moreover, as reported in our study, the decision to provide chemoprophylaxis was typically made after 6 days, by which time clinicians will know whether a patient will stay an additional day. Ultrasound assessment was performed in only 15% of patients but, to our knowledge, no data on current practice relating to such use of ultrasound are available. Assessment of the occurrence of ICH episodes was performed for the duration ICU admission but not for the period after discharge from ICU. Most CT scans were performed early during ICU admission, creating clinical practice-dependent ascertainment bias. Moreover, we did not measure volume changes in ICH. However, it is unlikely that, in the presence of clinical deterioration, a head CT scan would not have been needed at any time during ICU stay. Thus, the lack of later CT scans implies lack of clinical deterioration. In addition, while we use the term secondary ICH, some of these ICHs may represent the evolution of the appearance of the brain after the primary trauma rather than actual secondary events. Finally, by showing that essentially all secondary ICH episodes occurred by Day 2, most major surgery occurred by Day 3 and essentially all VTE episodes occurred after Day 6, our study provides preliminary evidence for a likely safe window for chemical VTE prophylaxis initiation and/or ultrasound surveillance.

## Conclusion

We conducted a retrospective analysis of current VTE prophylaxis practice in TBI patients with prolonged ICU stay, a unique group that had not previously been specifically studied. We conducted a highly granular analysis and demonstrated a relatively high incidence of VTE that manifested clinically and was radiologically confirmed during ICU and hospital admission, despite generally ubiquitous mechanical prophylaxis. We also demonstrated that secondary ICH was essentially a complication of the first 2–3 days and was radiologically assessed as being of limited magnitude in most cases. In contrast, VTE was almost always a complication that occurred after Day 6 and mostly manifested as PE. These findings provide important epidemiological information and provide a rationale for use of VTE chemoprophylaxis (after Day 3 and before Day 6) and/or scheduled lower limb ultrasound surveillance (beginning by Day 6) for TBI patients.

## Competing interests

No relevant disclosures.

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doi: https://doi.org/10.51893/2021.4.OA1

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