

## INPLASY

INPLASY2026100017

doi: 10.37766/inplasy2026.10.0017

Received: 2 October 2026

Published: 3 October 2026

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**Author Affiliation:**David Geffen School of Medicine,  
UCLA.**Early Pharmacologic VTE Prophylaxis in Traumatic Brain Injury Demonstrates Reduced Thromboembolic Events Without Increased Hemorrhagic Progression**

Liff, L; Kim, J; Mekonnen, M; Li, A; Yang, I.

**ADMINISTRATIVE INFORMATION****Support** - None.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100017**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 October 2026 and was last updated on 3 October 2026.**INTRODUCTION**

**Review question / Objective** How does early VTE prophylaxis impact VTE development, ICH progression, and mortality compared to late VTE prophylaxis?

**Rationale** There is currently a lack of consensus on optimal timing of VTE prophylaxis especially in regards ICH expansion, we conducted a meta analysis to clarify the latest clinical evidence to support enhanced recommendations about heparin timing in the broader TBI population.

**Condition being studied** TBI confers an increased risk of VTE development, however there is also concern for ICH progression and mortality risk associated with VTE prophylaxis. We looked into VTE development, ICH progression, and mortality with early vs late heparin prophylaxis.

**METHODS**

**Search strategy** PUBMED: ("Traumatic Brain Injury\*" OR "Craniocerebral Trauma" OR "Cerebral Trauma" OR "Cerebrovascular Trauma" OR "Head Injury" OR "Head Trauma" OR "Brain Trauma\*" OR "Concussion\*" OR "Brain Contusion\*" OR "Cerebellar Contusion\*" OR "Cerebral Contusion\*" OR "Traumatic Cerebral Lesion\*" OR "Traumatic Brain Lesion\*") AND (heparin OR enoxaparin OR tinzaparin OR dalteparin)  
cochrane: ((Brain NEXT (Contusion\* OR Trauma\*)) OR (Cereb\* NEXT (Contusion\* OR Concussion\* OR Contusion\* OR trauma)) OR (Concussion\*) OR "posttraumatic encephalopathy" OR ("traumatic brain" NEXT injur\*) OR (head NEXT (trauma OR injury)) OR "traumatic brain lesion" OR "traumatic cerebral lesion") AND (heparin OR enoxaparin OR tinzaparin OR dalteparin)  
Embase: ('traumatic brain injury\*' OR 'craniocerebral trauma'/exp OR 'craniocerebral trauma' OR 'cerebral trauma'/exp OR 'cerebral

trauma' OR 'cerebrovascular trauma'/exp OR 'cerebrovascular trauma' OR 'head injury'/exp OR 'head injury' OR 'head trauma'/exp OR 'head trauma' OR 'brain trauma\*' OR concussion\* OR 'brain contusion\*' OR 'cerebellar contusion\*' OR 'cerebral contusion\*' OR 'traumatic cerebral lesion\*' OR 'traumatic brain lesion\*') AND ('heparin'/exp OR heparin OR 'enoxaparin'/exp OR enoxaparin OR 'tinzaparin'/exp OR tinzaparin OR 'dalteparin'/exp OR dalteparin)

web of science: ("Traumatic Brain Injury" OR "Craniocerebral Trauma" OR "Cerebral Trauma" OR "Cerebrovascular Trauma" OR "Head Injury" OR "Head Trauma" OR "Brain Trauma" OR "Concussion" OR "Brain Contusion" OR "Cerebellar Contusion" OR "Cerebral Contusion" OR "Traumatic Cerebral Lesion" OR "Traumatic Brain Lesion") AND (heparin OR enoxaparin OR tinzaparin OR dalteparin)

Scopus: Search Criteria:ALL ( "traumatic brain injury\*" OR "craniocerebral trauma" OR "cerebral trauma" OR "head injury" OR "head trauma" OR "brain trauma\*" OR "concussion\*" OR "brain contusion\*" OR "cerebellar contusion\*" OR "cerebral contusion\*" OR "traumatic cerebral lesion\*" OR "traumatic brain lesion\*" ) AND ALL ( heparin OR enoxaparin OR tinzaparin OR dalteparin ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) OR LIMIT-TO ( DOCTYPE , "cp" ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) ) AND ( EXCLUDE ( EXACTKEYWORD , "Nonhuman" ) OR EXCLUDE ( EXACTKEYWORD , "Animals" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Experiment" ) OR EXCLUDE ( EXACTKEYWORD , "Child" ) OR EXCLUDE ( EXACTKEYWORD , "Infant" ) ).

**Participant or population** Non pediatric, and non-pregnant patients with moderate to severe TBI.

**Intervention** Early (<72hrs) initiation of heparin-based VTE prophylaxis.

**Comparator** Late (72 hours or greater) initiation of heparin-based VTE prophylaxis.

**Study designs to be included** Observational studies and RCTs.

**Eligibility criteria** Adult patients (age  $\geq 18$  years) with traumatic brain injury; compared early versus late initiation of heparin-based VTE prophylaxis; reported at least one of the pre-specified outcomes (VTE development, ICH progression, mortality, or ICU/hospital LOS).

**Information sources** Embase, Scopus, Web of Science, PubMed, and Cochrane.

**Main outcome(s)** VTE development, ICH progression, and mortality.

**Additional outcome(s)** ICU and hospital LOS.

**Data management** Search results were screened for eligibility based on predefined inclusion and exclusion criteria. Data from included studies were extracted onto a spreadsheet and verified for accuracy. Extracted variables included sample size, patient demographics (age, sex, GCS score), heparin type and dose (if available), timing of initiation, and outcomes including VTE development, ICH progression, mortality, and hospital and ICU length of stay.

#### Quality assessment / Risk of bias analysis

Statistical assessment of potential publication bias and study distribution was performed using funnel plots. Separate funnel plots were created for each outcome of interest (mortality, VTE development, and ICH progression). Each study was plotted as a single point and labeled using the first author's name and year of study. The graphs plot our estimate of effect against the precision of the study. They were examined visually for clustering, heterogeneity, and symmetry.

#### Strategy of data synthesis

Analyses were performed in R using the meta and metafor packages. All analyses used random-effects models to account for anticipated clinical and methodological heterogeneity across study populations, injury severities, and institutional practices. For binary outcomes (VTE development, ICH progression, and in-hospital mortality), the primary comparative analysis used a standardized 72-hour binary classification of heparin initiation timing, with arms initiating heparin within 72 hours of injury classified as early and those initiating at 72 hours or beyond classified as late. Statistical heterogeneity was assessed using the  $I^2$  statistic and Cochran's Q test.  $I^2$  values of 25%, 50%, and 75% were interpreted as thresholds for low, moderate, and high heterogeneity, respectively. A two-sided significance threshold of  $p < 0.05$  was applied throughout.

**Subgroup analysis** No formal subgroup analyses were pre-specified. Post-hoc exploratory meta-regression analyses were conducted to examine the influence of baseline GCS score, age, and sex as potential confounders of the primary effect estimates.

**Sensitivity analysis** Comparison of  $\tau^2$  estimation methods (DerSimonian-Laird vs REML) to assess

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robustness of significance thresholds. No formal leave-one-out analysis was conducted.

**Language restriction** Non-English articles will be excluded.

**Country(ies) involved** United States of America.

**Keywords** Traumatic brain injury (TBI), Venous thromboembolism (VTE), Intracerebral hemorrhage (ICH), Pharmacologic prophylaxis, Early prophylaxis, Heparin prophylaxis.

**Contributions of each author**

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