

A Systematic Review of the Risks and Benefits of Venous Thromboembolism Prophylaxis in Traumatic Brain Injury

Joseph Margolick, Charlotte Dandurand, Katrina Duncan, Wenjia Chen,
David C. Evans, Mypinder S. Sekhon, Naisan Garraway,
Donald E. G. Griesdale, Peter Gooderham, S. Morad Hameed

ABSTRACT: Background: Patients suffering from traumatic brain injury (TBI) are at increased risk of venous thromboembolism (VTE). However, initiation of pharmacological venous thromboprophylaxis (VTEp) may cause further intracranial hemorrhage. We reviewed the literature to determine the postinjury time interval at which VTEp can be administered without risk of TBI evolution and hematoma expansion. **Methods:** MEDLINE and EMBASE databases were searched. Inclusion criteria were studies investigating timing and safety of VTEp in TBI patients not previously on oral anticoagulation. Two investigators extracted data and graded the papers' levels of evidence. Randomized controlled trials were assessed for bias according to the Cochrane Collaboration Tool and Cohort studies were evaluated for bias using the Newcastle-Ottawa Scale. We performed univariate meta-regression analysis in an attempt to identify a relationship between VTEp timing and hemorrhagic progression and assess study heterogeneity using an I^2 statistic. **Results:** Twenty-one studies were included in the systematic review. Eighteen total studies demonstrated that VTEp postinjury in patients with stable head computed tomography scan does not lead to TBI progression. Fourteen studies demonstrated that VTEp administration 24 to 72 hours postinjury is safe in patients with stable injury. Four studies suggested that administering VTEp within 24 hours of injury in patients with stable TBI does not lead to progressive intracranial hemorrhage. Overall, meta-regression analysis demonstrated that there was no relationship between rate of hemorrhagic progression and VTEp timing. **Conclusions:** Literature suggests that administering VTEp 24 to 48 hours postinjury may be safe for patients with low-hemorrhagic-risk TBIs and stable injury on repeat imaging.

RÉSUMÉ: Revue systématique des risques et des bénéfices de la prophylaxie des tromboembolies veineuses chez les patients atteints d'une lésion cérébrale traumatique. Contexte: Les patients qui ont subi une lésion cérébrale traumatique (LCT) présentent un risque accru de tromboembolie veineuse (TEV). Cependant, l'amorce de la thromboprophylaxie veineuse pharmacologique (TEVp) peut aggraver une hémorragie intracrânienne. Nous avons revu la littérature afin de déterminer le moment après le traumatisme où la TEVp peut être administrée sans risque de provoquer une évolution de la TEV et une expansion de l'hématome. **Méthodologie:** Nous avons effectué une recherche dans MEDLINE et dans EMBASE pour identifier des études sur le moment où la TEVp avait été administrée et la sécurité de la TEVp chez des patients atteints d'un LTC qui ne prenaient pas d'anticoagulants oraux antérieurement. Deux chercheurs ont recueilli les données et évalué le niveau de preuve. Le *Cochrane Collaboration Tool* a été utilisé pour détecter les biais dans les études contrôlées et randomisées et l'échelle de Newcastle-Ottawa a été utilisée pour évaluer les biais dans les études de cohorte. Nous avons eu recours à une analyse de méta-régression univariée pour tenter d'identifier une relation entre le moment où la TEVp avait été administrée et la progression de l'hémorragie et nous avons évalué l'hétérogénéité des études au moyen de la statistique I^2 . **Résultats:** Vingt-et-une études ont été incluses dans cette revue systématique. Dans dix-huit études, la TEVp administrée après le traumatisme chez des patients dont le scan à la tomodensitométrie de la tête était stable n'avait pas provoqué de progression de la LTC. Selon 14 études, l'administration de la TEVp 24 à 72 heures après le traumatisme est sûre chez les patients dont la lésion est stable. Quatre études suggéraient que l'administration de la TEVp dans les 24 heures de la blessure, chez les patients dont la LTC est stable, n'entraîne pas de progression d'une hémorragie intracrânienne. Globalement, l'analyse de méta-régression a démontré qu'il n'existait pas de relation entre le taux de progression de l'hémorragie et le moment d'administration de la TEVp. **Conclusions:** Selon la littérature, la TEVp peut être administrée sans danger 24 à 48 heures après un traumatisme chez les patients dont le risque d'hémorragie est faible et la lésion s'avère stable à l'imagerie.

Key words: Venous thromboembolism, Head Trauma, Chemoprophylaxis

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From the From the Department of Surgery, Divisions of General Surgery (JM, KD, DCE, NG, SMH); Neurosurgery (CD, PG); Department of Medicine, Division of Critical Care (DEGG, MSS), Faculty of Pharmaceutical Sciences (WC)*, University of British Columbia, Vancouver, British Columbia, Canada.

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Correspondence to: S. Morad Hameed, Department of Surgery, University of British Columbia, Trauma Services 855 W 12th Ave Vancouver, BC, V5Z 1M9. Email: morad.hameed@vch.ca.

Traumatic brain injury (TBI) is associated with 50,000 deaths and nearly 300,000 hospitalizations annually in the United States,¹ and is the worldwide leading cause of mortality in patients between the ages of 25 and 44.² There is also a significant social cost associated with brain injury because more than 5 million Americans live with long-term neurological sequelae stemming from TBI.³

Patients with TBI are at an increased risk of venous thromboembolism (VTE), defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE). Studies have reported a baseline VTE risk of approximately 5% in all hospitalized patients⁴; however, for TBI patients, the risk of DVT is approximately 30% to 60%.^{2,5-12} DVT can pose significant danger to patients because roughly 20% to 30% of calf DVTs will extend proximally to the thigh if left untreated, of which approximately 40% will result in PE.¹³ Overall, PEs occur in 1% to 24% of trauma patients.^{2,7,14,15} Furthermore, DVTs may cause post-thrombotic syndrome and chronic venous stasis, which can significantly affect patients' quality of life.⁸ The exact etiology of the more than fourfold increased rate of DVTs in TBI patients is not entirely clear¹¹; however it is thought that TBIs exert a dampening effect on the physiologic dynamics of fibrinolysis, which, when coupled with the immobility caused by prolonged hospitalization creates a highly pro-thrombotic state.¹⁶⁻¹⁸

Pharmacological venous thromboprophylaxis (VTEp) is effective in reducing rates of VTE^{2,17}; however, some literature suggests that VTEp increases the risk of intracranial hemorrhage (ICH) progression^{19,20}; therefore, many physicians are hesitant to administer VTEp for fear of causing secondary progression of TBI.¹⁷ Unfortunately, this delay may cause undue risk from VTE. Clinical decisions must therefore balance the risk of VTE with the potential to cause iatrogenic ICH progression.

There is currently insufficient research to produce formal clinical guidelines on optimal timing of VTEp.^{9,21} In 2002, the Eastern Association for the Surgery of Trauma (EAST) recommended that the safety of VTEp, both low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) in TBI was not established and VTEp administration should be tailored to each patient.²² Similarly, both the American College of Chest Physicians (ACCP) and Brain Trauma Foundation (BTF) recommend VTEp in lieu of mechanical prophylaxis as soon as possible after sustaining a TBI, but could not recommend a specific time frame within which VTEp can be safely administered.^{23,24}

Clinical decision tools for VTE prevention improve VTEp adherence, and the ACCP guidelines recommend formal VTE prevention protocols for hospitalized patients.²³ With this in mind, we set out to review the literature to determine the risk of TBI expansion after VTEp with the ultimate goal of determining how long clinicians should wait after TBI before administering VTEp. A secondary objective of this research was to lay the foundation for a clinical practice guideline (CPG) directing timing of VTEp therapy in TBI patients.

METHODS

The primary objective of this study is to determine the safety of administering VTEp (LMWH or UFH) to TBI patients, and in particular, assessing if VTEp causes intracranial hemorrhagic expansion. The outcome of interest is whether VTEp causes hemorrhagic progression in TBI patients, and if so, within what time frame postinjury. The population of interest includes all

hospitalized patients with TBI who were not on anticoagulation preinjury or known to have a preexisting coagulopathy. This systematic review was reported in accordance with the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses protocols.²⁵ The literature was searched using databases MEDLINE and EMBASE. We limited our findings to English language studies published between January 1, 1999, and December 1, 2015. A combination or partial combinations of the following search terms were used: traumatic brain injury, venous thromboembolism, anticoagulant agent, anticoagulants, fibrinolytic agent, prophylaxis, thromboprophylaxis, chemoprophylaxis, brain injuries, and venous thrombosis. (Please see the supplementary appendix for detailed search strategy.) Animal studies, articles about patients taking anticoagulants before TBI and articles on nontraumatic intracranial hemorrhage (hemorrhagic stroke) were excluded. Articles with short titles such as "Discussion" or "Author Reply" and those without an abstract were excluded. Titles of articles were first reviewed for relevance. Abstracts of selected articles were then reviewed for inclusion in the study. Two independent investigators (JM and CD) then evaluated full texts of selected articles. Reference sections of the articles were reviewed to identify additional relevant studies.

Two investigators (JM and CD) independently extracted data from the included studies and assessed the methodological quality based on the Oxford Centre for Evidence Based Medicine Levels of Evidence.²⁶ Each study was given an evidence class score ranging from 1a (high-quality randomized controlled trials [RCTs]) to 4 (case series and poor-quality case-cohort studies). A score of 1b was given to RCTs with narrow confidence intervals, 2a to systematic reviews with homogeneity, 2b to low-quality RCTs and retrospective cohort studies, 3a to systematic reviews with heterogeneity or case control studies, and 3b to individual case control studies. Data were extracted from the included studies using a standardized form. We collected authors, date of publication, journal of publication, a descriptive evaluation of each study, research design, timing of VTEp, study limitations, and main findings (Table 1). RCTs were assessed for bias based on the Cochrane Collaboration Tool²⁷ and cohort studies were evaluated for bias using the Newcastle-Ottawa Scale.²⁸

Statistical analyses were performed using Stata 12.1 software package (College Station, TX). Pooled rate estimates from the studies were plotted against VTEp timing (i.e. no VTEp vs VTEp given within 24 hours of injury, 48 hours of injury, 72 hours of injury, and >72 hours after injury). We performed univariate meta-regression analysis in an attempt to identify a relationship between VTEp timing and hemorrhagic progression and assess study heterogeneity (variance between studies) using an I^2 statistic.

After the formal literature review, a consultation process with two trauma surgeons, two intensivists, and a neurosurgeon was carried out to review the literature findings. The consultation process occurred over several meetings and involved reviewing all available literature. Expert opinion, based on years of clinical work in trauma, critical care, and neurosurgery, was used to supplement the data from the review and to attain consensus opinion on a CPG.

RESULTS

Eighty-one articles from the MEDLINE database and 332 from the EMBASE database were selected for abstract review

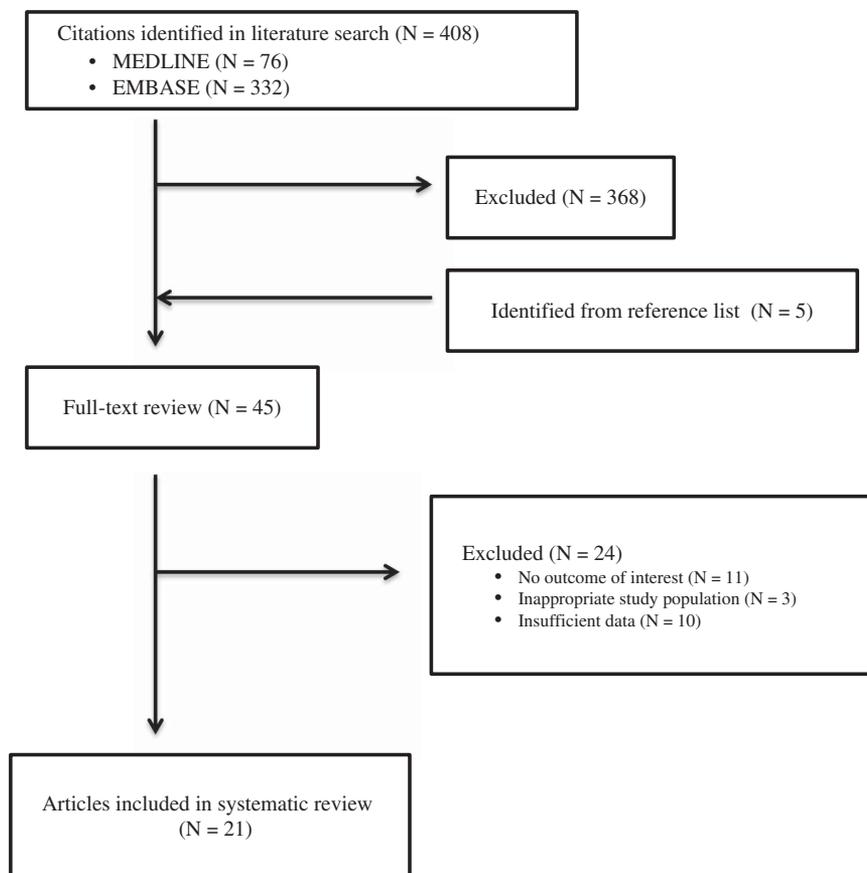


Figure 1: Methods Flow Diagram

(Figure 1). Forty-five articles were reviewed in entirety, of which 21 were included in the systematic review. Reasons for exclusion after full review were: no data regarding VTEp^{29,30} data from rehabilitation centers,^{31,32} no data on TBI progression,^{11,13,20,21,33,34} investigating patients on oral anticoagulation before arriving in the hospital,³⁵ published critique of previous article,³⁶ literature reviews of studies already captured by our review,^{2,3,8,9,12,18,37-39} no data on timing of VTEp,⁴⁰ and a study investigating inferior vena cava (IVC) filters.¹⁴

Eighteen total studies demonstrated that VTEp postinjury in patients with stable head computed tomography (CT) scan does not lead to radiographic or clinical TBI progression. Fourteen studies demonstrated that VTEp administration specifically 24 to 72 hours postinjury is safe in patients with stable injury. Four studies suggested that administering VTEp specifically within 24 hours of injury in patients with stable TBI does not lead to progressive ICH. However, one study, a retrospective review with multivariate analysis of 1215 patients, suggested LMWH is a risk factor for TBI progression, defined as “progressive bleed on follow up CT scan,”⁴¹ and another retrospective review found UFH was associated with higher rates of TBI progression, defined as worsening bleeding on repeat CT head, than LMWH.⁴² A study by Lin et al divided TBIs into those with ICH and without ICH. They determined that the rate of ICH progression when VTEp was administered within 48 hours was 10.6% in those with preexisting ICH compared with 0.7% in those without ICH.⁴³

Meta-regression analysis of the studies demonstrated that there was no relationship between rate of hemorrhagic progression and

VTEp timing. Overall, the timing of DVT prophylaxis only explains 1.56% of the variations between rebleeding rates reported in different studies, which is not statistically significant ($p=0.31$). Because of the high level of heterogeneity (variation between studies, $I^2 >95\%$) detected by the meta-analysis, we did not report weighted-pooled summary estimates for rebleeding rate in this review. Four of 12 studies directly comparing VTE rates between early and late VTEp administration reported a significant decrease in VTE rates with early VTEp administration.^{17,41,46,47} Similarly, another seven studies found VTEp rates of only 0.0% and 2.0% in patients given VTEp within 24 to 72 hours of injury. Three other retrospective reviews found somewhat higher rates of VTE that ranged from 7.3% to 14%.^{21,54,57} Summary of literature can be found in Table 1; see Table 2 for risk of bias assessment of RCTs based on the Cochrane Collaboration tool.²⁶ Only seven of the 18 nonrandomized cohort studies reviewed were deemed “low risk” for bias according to Newcastle-Ottawa Scale (Table 3).²⁷ A preliminary CPG was formulated based on data from this review and consensus opinion among clinical experts (Figure 2).

DISCUSSION

TBI is a common cause of death and disability in young patients.² Preventing secondary brain injury is the primary objective of TBI management, yet complications of VTE can be devastating. Clinicians should be wary of iatrogenic hemorrhagic progression secondary to VTEp; however, delaying chemoprophylaxis may cause unwarranted increases in morbidity and

Table 1: Systematic review of 21 studies

Manuscript	EC	Research design	Timing of VTEp	TBI progression	Limitations	Findings and conclusion
Kim et al, 2014 ¹ N = 75	2b	Retrospective cohort study	Early: <72 hours postadmission Intermediate: 72-120 hours Late: >120 hours post admission LMWH or UFH	Head CT scans from all three groups worsened during first 24 hours, but stabilized thereafter. Early VTEp increased rate of radiographic stabilization	Retrospective Small sample size	Early VTEp group improved clinically faster than the late group (p < 0.05) VTEp increases rate of TBI stabilization when given within 72 hours of injury No difference in TBI severity (radiographic or clinical) between groups
Farooqui et al, 2013 ⁴⁶ N = 236	2b	Retrospective cohort study	Preprotocol group: no protocol, VTEp based on individual clinical decision Protocol group: VTEp within 24 hours of admission if stable repeat CT scan of the head LMWH or UFH	3/107 (2.8%) had progression of ICH during preprotocol study period 1/129 (0.7%) had progression of ICH with early VTEp protocol	Retrospective Protocol noncompliance	No significant difference in progression of ICH with protocol: 0.7% vs 2.8% preprotocol). DVT rates lower in protocol group lower (0.0%) compared with preprotocol group (5.6%, p < 0.05) VTEp within 24 hours of admission and stable TBI is safe and effective
Jamjoom and Jamjoom, 2013 ¹⁷ N = 1624 (5 studies)	2a	Metaanalysis	Early: <72 hours postadmission Late: >72 hours postadmission LMWH or UFH	Pooled data of three studies demonstrated that early VTEp had RR and 95% CI of 0.64 (0.35-1.14) for developing TBI progression	Heterogeneous studies Selection bias: patients with severe ICH or progression included in late group	Patients in the early group had almost half the number of VTEs, with RR of 0.52 No difference in ICH progression between early and late groups
Nickele et al, 2012 ⁵⁰ N = 135	2b	Cohort study	Control: Mean time to VTEp = 4.9 days postadmission. Individual clinical decisions Protocol: VTEp 24 hours after stable repeat head CT scans (mean time to VTEp, 3.4 days) LMWH or UFH	No VTEp related progression of ICH	Not randomized Protocol non-compliance Small sample size	No difference between control and protocol group in incidence of DVT (4.2% vs 6.9%) or PEs (4.2% vs 5.75%) No patients required their VTEp to be stopped due to TBI expansion. No significant difference in ICH progression between control and protocol groups.
Phelan et al. 2012 ⁵¹ N = 62	2b	RCT; noninferiority trial	Control: placebo SC BID 24 hours after stable repeat CT scan of the head Intervention: Enoxaparin 30 mg SC BID 24 hours after stable repeat CT scans of the head	5.9% of patients had radiographic progression on scans performed 24 hours after commencement of VTEp vs 3.6% in the placebo group (not significant)	Small sample size No routine VTE screening with Doppler ultrasound	No significant difference in radiographic TBI progression compared with control Any radiographic progression seen was not associated with clinical progression of TBI One patient (3.5%) had DVT in placebo group
Saadeh et al, 2012 ¹⁰ N = 122	2b	Retrospective case series	Early: VTEp started 24-48 hours after stable CT scan of the head Late: VTEp started >48 hours after stable CT scan of the head LMWH or UFH	No patients who received VTEp (n = 93) had progression of ICH	Retrospective Small sample size	No patients developed VTE VTEp within 24-48 hours of a radiographically stable TBI is safe
Minshall et al, 2011 ⁴² N = 386	2b	Retrospective cohort study	VTEp initiated once stable CT of the head is complete UFH 5000 U TID; Mean time to initiation was 47 hours postadmission LMWH (enoxaparin 30 mg BID): Mean time to initiation was 54 hours postadmission	LMWH group: rate of ICH progression was 5% UFH group: rate of ICH progression was 12%	Retrospective Selection bias: head AIS and ISS significantly higher in UFH group 8% of patients in each group had progression of ICH before initiation of VTEp	UFH group had significantly more PEs (3.7%) than LMWH group (0.0%), p < 0.05. Rates of isolated DVT were 1% in each group Higher rate of ICH progression in the UFH group than the LMWH group (p < 0.05)
Scudday et al, 2011 ⁴⁷ N = 812	2b	Retrospective cohort study	Prophylaxis group: VTEp within 24-72 of stable CT scan of the head No prophylaxis group: no VTEp LMWH or UFH	6% in the no prophylaxis group had TBI progression versus 3% in the prophylaxis group, p = 0.05	Retrospective Variability of VTEp timing Routine screening of VTE in the no prophylaxis group only Selection bias: prophylaxis group significantly more injured	The prophylaxis group was more injured (ISS of 23.8 vs 16.6, p < 0.01) and had more patients with GCS < 9 (185 vs 115, p < 0.01). Patients in the prophylaxis group had significantly fewer VTEs (1.0% vs 3.0%, p < 0.05) VTEp safe and effective

Table 1. *Continued*

Manuscript	EC	Research design	Timing of VTEp	TBI progression	Limitations	Findings and conclusion
Kwiatk et al, 2012 ⁴¹ N = 1215	2b	Retrospective cohort study	Early: VTEp < 48 hours postadmission Intermediate: 48 hours-7 days postadmission Late: >7 days postadmission No prophylaxis	TBI progression Early: 22.2% Intermediate: 12.6% Late: 14.9% No VTEp: 24%	Retrospective Selection bias: LMWH group had more severe injury on admission than no prophylaxis group	Timing of LMWH did not affect TBI progression 10% of patients had TBI progression after VTEp LMWH strongest risk factor for TBI progression (OR, 2.41; 95% CI, 1.65-3.53)
Salottolo et al, 2011 ⁵² N = 480	2b	Retrospective cohort study	Early: initiation of VTEp <72 hours postadmission Late: Initiation of VTEp >72 hours postadmission LMWH or UFH	Early VTEp group: 6.5% rate of TBI progression Late VTEp group: 14.3% rate of TBI progression No VTEp group: 8.5% rate of TBI progression	Retrospective Unclear definition of TBI progression	TBI progression did not differ between patients receiving early, late or no VTEp, p = 0.92 15 patients (3.1%) developed VTE. Neither VTEp administration nor timing of VTEp were independent predictors of VTE
Callcut et al, 2011 ⁵³ N = 77	2b	Retrospective case series	Therapeutic IV UFH or ASA started on median day 3 after admit (roughly 24-48 hours after stable repeat CT scan of the head) Treated group: ASA or therapeutic UFH Untreated group: SC prophylactic UFH or no treatment	No significant difference in radiographic TBI progression between treated group (5.1%) and untreated group (6.3%)	Retrospective VTE rates not measured Small sample size VTEp with SC UFH considered in the untreated group	Rates of TBI progression not significantly different in patients treated with IV UFH, ASA, VTEp, or no VTEp
Koehler et al, 2011 ⁴⁹ N = 669	2b	Retrospective cohort study	Early: VTEp <72 hours postadmission (mean, 2.7 days) Late: VTEp >72 hours (mean, 5.3 days)	1.5% had TBI progression after VTEp in early group 1.5% had TBI progression after VTEp in late group	Retrospective Selection bias: rates of TBI progression before initiation of VTEp was significantly higher in late group	1.5% of patients developed VTEs in early group versus 3.5% in late group, p = 0.117 No significant difference in ICH progression between early and late VTEp groups across all injury types
Norwood et al, 2008 ⁶ N = 525	3	Prospective observational	VTEp group: all patients received VTEp within 48 hours of admission (mean time, 36.2 hours) Enoxaparin 30 mg BID	Progressive hemorrhage in 3.4% if patients after administering VTEp 8.3% of patients had ICH progression at baseline Had there been no protocol violations, rate of TBI progression after VTEp would have been 1.8% 56% of TBI progressions resulting from protocol violations	Nonrandomized, observational Protocol violations: 5 of 6 patients with clinically significant TBI progression were due to protocol violations	VTE rate of 1.14% (no PEs) 12 of 18 patients who had TBI progression were considered clinically insignificant If protocol followed closely, VTEp can be administered within 48 hours of admission with low risk of clinically significant TBI progression
Dudley et al, 2010 ⁵⁴ N = 287	2b	Retrospective cohort study	VTEp 48-72 hours after injury if stable repeat head CT scan Enoxaparin 30 mg BID* Or dalteparin 5000 U daily	1 patient (0.4%) had TBI progression 2 weeks postadmission	Retrospective Follow-up CT scans were not done systematically; only if clinically warranted	VTE rate of 7.3% (3.1% proximal DVTs) No difference in VTE rate between enoxaparin and dalteparin (7.0 vs 7.5% p = 0.87) Very low risk of TBI progression after early administration of VTEp
Lin et al, 2013 ⁴³ N = 3812	2b	Retrospective cohort study	Within 48 hours of injury if stable CT head UFH	10.6% of patients with ICH had radiographic progression if given UFH within 48 hours 0.7% of patients with TBI without ICH had radiographic progression (developed ICH) if given UFH within 48 hours	Retrospective Poor protocol compliance Did not define ICH or TBI progression Dosing of UFH not in accordance with North American norms (5000 U TID)†	UFH protocol did not decrease incidence of VTE (0.97% vs 1.24%, p = 0.492) TBI, defined by AIS >3 without ICH, has a very low rate of progression secondary to VTEp compared with patients with ICH
Kleindienst et al, 2003 ⁴⁸ N = 344	2b	Retrospective cohort study	344 TBI patients had VTEp within 24 hours of admission or surgery if repeat CT scan of the head is stable Certoparin 18 mg daily	9 patients (3.2%) had progression of ICH No nonoperative TBI patients had ICH progression	Retrospective No control or comparison group Largely composed of patients requiring neurosurgical evaluation	No patients were diagnosed with VTE 3.2% rate of progression; all patients recovered well All patients with ICH progression were postoperative from neurosurgical intervention Early VTEp safe in nonsurgical TBI patients

Norwood et al, 2002 ⁵⁵ N = 177	3	Prospective observational	VTEp within 24 hours of admission Enoxaparin 30 mg BID*	6 patients (4%) of patients had ICH progression after administration of enoxaparin. Two of the 6 patients were postoperative ICH progression found in 28 patients (19%) before initiation of VTEp. Enoxaparin was still given in these patients and there were no further ICH progression	No control or comparison group Protocol violation: 2 of the 6 patients with TBI progression were protocol violations	DVT rate, 2% LMWH does not increase the rate of ICH progression when given to patients with radiographically progressing TBI A significant decrease in rate of progression of ICH after 24 hours and administration of VTEp, p = 0.002
Levy et al, 2010 ¹⁹ N = 340	2b	Retrospective cohort study	Early: VTEp <72 hours postadmission Late: VTEp >72 hours postadmission No treatment: No VTEp administered Enoxaparin 30 mg BID	7.3% of patients with initially stable head CT scans had progression. Neither timing nor VTEp exposure associated with progression 92 patients had ICH progression before initiation of VTEp. The greatest predictor of further progression after unstable CT scan of the head was VTEp administration (OR, 13.1; 95% CI, 1.6-103.4)	Retrospective Selection bias: 60% with VTEp had severe TBI versus 12% in no treatment group 73 patients had their VTEp stopped then restarted	Administration of VTEp does not increase risk of ICH progression in those with a stable CT scan of the head Conversely, in patients with progressive ICH, VTEp is associated with 13-fold increased in odds of developing further ICH progression
Kurtoglu et al, 2004 ⁵⁶ N = 120	2b	RCT	Determined by neurosurgery and trauma staff after CT scan of the head 24 hours postinjury Enoxaparin 40 mg daily	LMWH group: 2.0% had progression of ICH IPC group: 2.0% had progression of ICH‡	Not truly randomized Not clear exactly when VTEp started Enoxaparin dosing not standard for North America	No difference in ICH progression between LMWH and IPC group 6.6% developed DVTs and 3.3% developed PEs in IPC group versus 5.0% and 6.6% in LMWH group
Depew et al, 2008 ²¹ N = 124	2b	Retrospective cohort study	Early: VTEp <72 hours postadmission Late: VTEp >72 hours postadmission No treatment: No VTEp LMWH or UFH	Early group: 3.0% TBI progression Late group: 4.0% TBI progression No treatment: 0% progression	Retrospective Selection bias: no between-group comparison	Early group had VTE rate of 14% versus 11% in the late group and 0.0% in the no treatment group LMWH is safe with stable TBI
Kim et al, 2002 ⁵⁷ N = 64	2b	Retrospective cohort study	Early: VTEp <72 hours postadmission Late: VTEp >72 hours postadmission UFH 5000 U BID	No patients in early group had TBI progression	Retrospective Small sample size CT scans after initiation of VTEp were obtained in only 88% of study population	No significant difference in VTE between early and late groups (8.5% vs 6%) Early VTEp is safe and does not exacerbate intracranial injury

AIS = Abbreviated Injury Score; ASA = aspirin; BID = 2 times daily; CI = confidence interval; IPC = intermittent pneumatic compression; ISS = Injury Severity Score; IV = intravenous; OR = odds ratio; RR = risk ratio; SC = subcutaneously; TID = 3 times daily.

*Twice a day dosing.

†Dosing every 8 hours.

‡Intermittent pneumatic compression.

Table 2: Cochrane Collaboration Tool for assessing risk of bias for randomized controlled trials

Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcomes assessment (detection bias) (patient-reported outcomes)		
Blinding of outcomes assessment (detection bias) (all-cause mortality)		
Incomplete outcome data (attrition bias) (short term, 2-6 weeks)		
Incomplete outcome data (attrition bias) (long-term, >6 weeks)		
Selective reporting (reporting bias)		

-  Low risk of bias
-  High risk of bias
-  Unsure risk of bias

mortality. Decisions regarding VTEp timing are largely based on individual experience because ACCP, BTF, and EAST guidelines are unable to support any recommendations regarding timing of VTEp initiation other than recommending that VTEp be initiated once hemorrhagic risk decreased.^{22,24}

The efficacy of chemoprophylaxis in preventing VTE in hospitalized patients is well established.⁴⁴ In trauma patients, delaying VTEp for 72 hours after injury doubles the risk of VTE,¹⁷ whereas delaying VTEp 96 hours after injury increases the risk threefold.⁴⁵ In our review, four studies demonstrated that early administration of VTEp is associated with decreased rates of VTE,^{17,41,46,47} whereas another seven studies identified VTE rates of only 0.0% and 2.0% in patients given VTEp within 24 to 72 hours of injury. This rate is much lower than commonly documented rates of VTE in TBI patients, further that early administration of VTEp reduces incidence of VTE. Three studies, however, found rates of VTE ranged from 7.3% to 14%, despite administering VTEp within 72 hours of injury.^{21,54,57} Although rates of VTE in these three studies are relatively high despite early VTEp administration, patients in these studies were subject to routine screening with Doppler ultrasound; therefore, clinicians likely discovered subclinical DVTs that might not have been identified in other studies.

There are no consensus guidelines to recommend preferred agent, dose, or timing of chemical VTEp. The BTF guidelines suggest either UFH or LMWH because both are efficacious²⁴; therefore, the decision of whether to use UFH or LMWH is largely based on practitioner and institution preference. LMWH has demonstrated superiority in PE prevention compared with UFH in large studies, however. For instance, a large, multicenter retrospective study on trauma patients demonstrated that LMWH was associated with nearly one-half the rate of PEs compared with UFH.⁵⁸ Additionally, LMWH is associated with decreased rates of heparin-induced thrombocytopenia.⁵⁹ As such, many trauma

centers, including ours, favor LMWH as the agent of choice for chemical prophylaxis; however, UFH has a shorter half-life and is more easily reversed and thus may be the preferred agent when risk of hemorrhagic TBI progression is at stake. Clearly, there is a need for large-scale randomized trials to definitively investigate the potential benefits of LMWH compared with UFH in the setting of TBI.

Our primary objective was to determine if administering VTEp within 24 to 72 hours of TBI is safe or is dangerously associated with intracerebral hemorrhagic progression. Although the majority of evidence is retrospective, our study demonstrated that the practice of early VTEp administration after TBI is generally safe. Specifically, our review identified 18 studies that demonstrated that administering VTEp to patients with stable injury demonstrated by repeat head CT scan does not lead to progression of TBI. For example, Farooqui et al⁴⁶ initiated a protocol in which all patients with TBI received either Enoxaparin or UFH 24 hours postinjury as long as patients were without coagulopathy or progressive hemorrhage seen on repeat head CT scan. Forty-eight to 72 hours after initiation of VTEp, all patients received a third CT scan of the head to assess for TBI progression. Investigators found that there were no significant differences in Glasgow Coma Scale (GCS) or hemorrhagic progression between patients who received early and late VTEp. The investigators also found that patients who received early VTEp had significantly shorter hospital stays (12.3 days vs 7.4 days, $p < 0.05$), shorter intensive care unit stays (9.2 days vs 5.0 days, $p < 0.001$), and fewer VTEs (5.6% vs 0.0%, $p < 0.01$) than those who were not included in the early VTEp protocol. However, the early (protocol) group had lower overall Injury Severity Scores than the nonprotocol group, thus potentially confounding these results. Similarly, Saadeh et al¹⁰ conducted a retrospective review of 122 TBI patients who were administered VTEp with LMWH 24 to 48 hours after stable head CT. Investigators found that none of the patients who received

Table 3: Newcastle-Ottawa Scale Assessment of bias for cohort studies

Study	Representativeness of cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration that outcome wasn't present at start of study	Comparability	Assessment of outcome	Was follow-up long enough?	Was follow-up adequate?	NOS quality score (Sum of starts)
Kim et al. 2002	•	•	•	•	**	•			7
Norwood et al. 2002	•		•	•		•			4
Kliendienst et al. 2003	•		•	•		•			4
Lin et al. 2013	•	•	•	•		•			5
Levy et al. 2010	•	•	•	•	**	•			7
Depew et al. 2008	•		•	•		•			4
Dudley et al. 2010	•	•	•	•		•			7
Norwood et al. 2008	•	•	•	•		•			5
Koehler et al. 2011	•	•	•	•		•			5
Callcut et al. 2011	•	•	•	•	**	•	•	•	9
Salottolo et al. 2011	•	•	•	•	**	•			7
Kwaitt et al. 2012	•	•	•	•	**	•			7
Scudday et al. 2011	•	•	•	•	**	•			7
Nickele et al. 2013	•	•	•	•		•			5
Minshall et al. 2011	•	•	•	•		•			5
Saadeh et al. 2012	•	•	•	•		•			5
Farooqui et al. 2013	•	•	•	•		•			5
Kim et al. 2014	•	•	•	•		•		•	6

Full mark for Newcastle-Ottawa Scale was 9 points. Scores ≥ 7 were considered high quality.

* The corresponding paper scores one point in this category.

** The corresponding paper scores two points in this category.

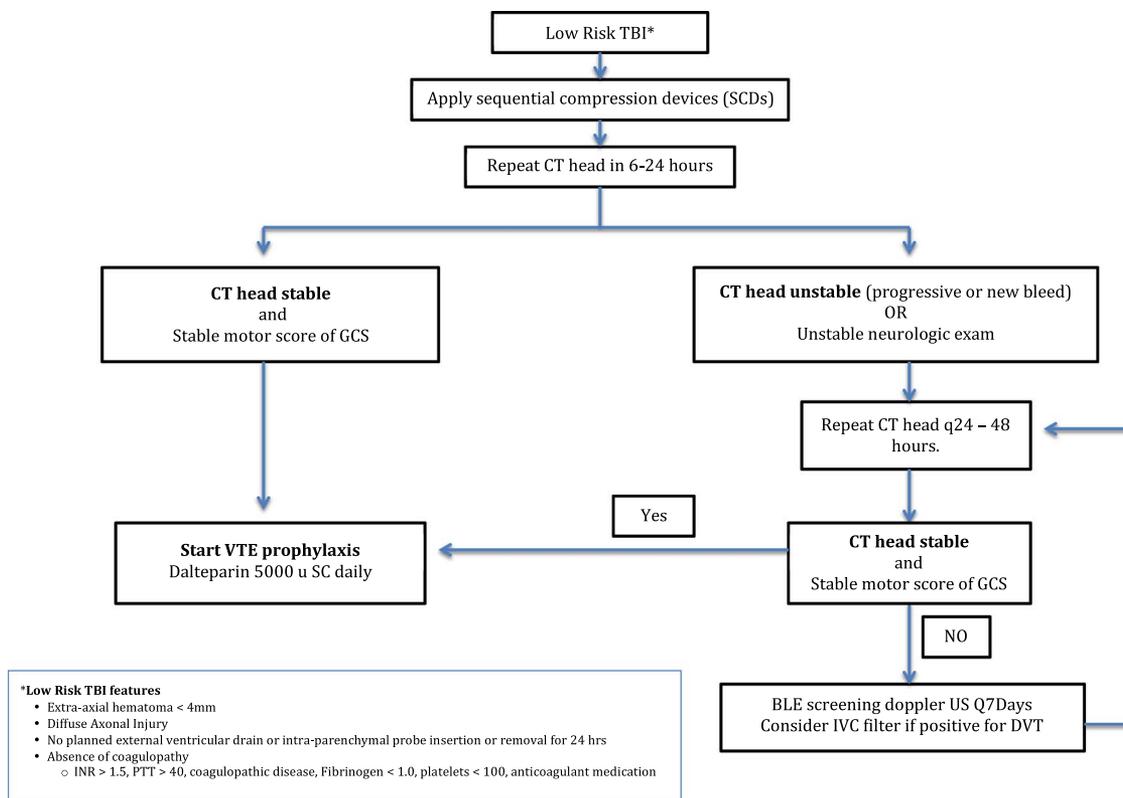


Figure 2: Clinical Practice Guidelines for Venous Thromboembolism Prophylaxis in Patients with low risk TBIs.

VTEp after TBI developed hemorrhagic progression; however, results from this study must be interpreted with caution because only 49.5% of eligible patients actually received VTEp within the 24- to 48-hour window. In a larger retrospective analysis study, Scudday et al⁴⁷ found that 242 of 402 TBI patients had VTEp administered 24 to 72 hours after stable head CT scans. In fact, patients administered early VTEp had significantly lower GCS and Abbreviated Injury Scale scores than those not administered VTEp. Interestingly, despite having more severe brain injury, there was no significant increase in hemorrhagic progression between patients receiving early VTEp (3% rate of progression) and patients not receiving VTEp (6% rate of progression).

The potential devastating morbidity and mortality associated with hemorrhagic TBI progression makes performing randomized prospective trials on VTEp initiation in TBI patients practically and ethically challenging; however, we did identify two prospective studies. A randomized, double-blinded, noninferiority clinical trial conducted by Phelan et al⁴⁹ demonstrated that administering VTEp within 48 hours of injury was associated with a TBI progression rate of 5.9%, which was not significantly different from placebo. The authors loosely defined TBI progression as a finding on repeat CT scans of the head of “worse” hemorrhage compared with the initial CT scan of the head. Interestingly, all radiographic TBI progressions were subclinical. The authors of this study limited their subjects to patients with TBIs deemed “low risk” for rebleeding, which were subdural hematomas or epidural hematomas smaller than 8 mm, intraventricular hemorrhage smaller than 2 cm, small contusions, and small subarachnoid hemorrhage with normal CT angiogram of the head and neck

vessels. This criteria, known as the Berne-Norwood Criteria, was conceived by Norwood et al in 2008.⁶ In their prospective cohort study, the authors enrolled “low-risk” TBI patients to receive VTEp within 48 hours of admission. Hemorrhagic progression was found in 18 (3.4%) patients after starting VTEp. Ten of the 18 total hemorrhagic transformations and five of the six clinically significant hemorrhagic transformations were from protocol violations. Had the protocol violations been withheld from the analysis, the rate of TBI progression after VTEp would have dropped to 1.8%. This study thus demonstrated that, in low rebleeding risk patients (as defined by the Berne-Norwood Criteria), VTEp can be administered safely within 48 hours of admission.

It is difficult to ascertain the natural history of TBIs and the baseline rate of hemorrhagic progression that occurs regardless of VTEp administration. For example, a retrospective cohort study by Kwiatt et al⁴¹ divided TBI patients into those who had received VTEp within 48 hours of admission, 48 hours to 7 days post-admission, and more than 7 days postadmission. The authors found that radiologic TBI progression occurred in 24% of patients who were not administered VTEp and that the rates of hemorrhagic progression did not increase once VTEp was given. In fact, there was no difference in the rate of hemorrhage progression after receiving VTEp regardless of when it was initiated. Of the patients who received VTEp within 48 hours, 22% had hemorrhage progression, which was similar to the rate of hemorrhagic progression in patients who had received LMWH 7 days postinjury, suggesting that timing of VTEp has no effect on TBI progression in this cohort. In total, 9.9% of patients with a stable repeat CT scan of the head before initiation of VTEp had progression after receiving

VTEp. In this series, multivariate analysis implicated VTEp as the strongest risk factor for hemorrhagic progression (odds ratio [OR], 2.41). This study included patients who required emergency neurosurgical intervention, which may explain the high baseline progression rate of 24%; however, deciphering which patients had TBI progression secondary to the natural history of TBIs regardless of LMWH is challenging.

That subtle hemorrhagic progression is frequently seen in repeat head CT scans indicates that subclinical progression is likely part of the natural history of TBIs. Furthermore, as CT scanning technology continues to improve, we are likely to continue identifying even more subtle changes in cerebral hemorrhage morphology. As such, the baseline rates of radiographic TBI progression in the absence of VTEp are variable. For example, Saddeh et al¹⁰ reported baseline hemorrhagic progression rate of 13.9%, Norwood et al (2002)⁵⁵ found a baseline progression rate of 19%, Callcut et al⁵³ found baseline progression rate at 6.25%, Scudday et al⁴⁷ reported a baseline progression rate of 6%, Phelan²⁰¹²⁵¹ found a rate of 3.5%, and Norwood et al (2008)⁶ determined that 8.3% of their subjects had progression at baseline. One potential explanation for the variance in baseline hemorrhagic progression is that timing of a second CT scan of the head differs between studies. It is quite plausible that a repeat CT scan of the head performed earlier is more likely to demonstrate baseline hemorrhagic progression than one that is performed later after the traumatic event. However, although the rates of baseline TBI instability vary according to the literature, it may be acceptable to deem VTEp “safe” if its administration does not cause the rate of TBI progression to rise significantly over the baseline.

Ultimately, data from our review indicate that early VTEp is safe in patients with TBI; however, most of the high hemorrhagic risk patients have been excluded from analysis. As a result, there is insufficient evidence to generalize VTEp safety in all TBI patients. We have created a preliminary CPG for use in patients with TBI and low hemorrhagic risk features (Figure 2). This CPG is based on our systematic review of the literature and expert consultations with intensivists, neurosurgeons, and trauma surgeons at a Canadian Level-1 trauma center. The CPG, which has not yet been implemented, places patients into two protocol arms: high hemorrhagic risk and low hemorrhagic risk. The CPG highlights the need for clinicians to weigh hemorrhage and thrombosis risk on a patient-by-patient basis. Early and systematic identification of those patients with low risk of delayed bleeding would allow early VTEp initiation and therefore reduce the risk of VTE in a substantial segment of the TBI population. Conversely, early classification of patients into a high hemorrhagic risk category would allow us to minimize the risk of iatrogenic TBI progression resulting from anticoagulation. Studies have shown that elevated prothrombin time and international normalized ratio, antiplatelet medications, and prior anticoagulants are risk factors for progression.⁶⁰⁻⁶² As a result, our CPG defines high hemorrhagic risk TBIs as extra axial hematomas > 4 mm, diffuse axonal injury, TBIs requiring neurosurgical intervention, and TBIs occurring in patients with an international normalized ratio >1.5, a partial thromboplastin time >40 seconds, a platelet count of <100 × 10⁹/liter, a known coagulopathy, and patients taking oral anticoagulants and/or anti-platelets medications. Patients with low hemorrhagic risk features and stable TBI would be allocated to a treatment pathway that supports administering VTEp with dalteparin 5000 units subcutaneously within 24 hours of injury.

Patients with unstable TBI and/or high hemorrhagic risk features would be shunted into a pathway that prioritizes mechanical VTEp, promotes early detection of DVT, and facilitates ongoing assessment hemorrhage risk based on serial head CTs. The BTF, EAST, and ACCP guidelines support the use of mechanical thromboprophylaxis with intermittent pneumatic compression whenever possible.^{22,24} Therefore, all patients in the high-risk arm of the CPG would be administered mechanical thromboprophylaxis. Our CPG would also recommend screening for DVTs clinically on daily rounds and every 7 days with Doppler ultrasound in patients in the high-risk arm in the hopes of more quickly identifying subclinical DVTs. Last, the EAST guidelines make Level III recommendations to consider IVC filters in trauma patients who cannot receive anticoagulation²²; therefore, our CPG also recommends consideration of an IVC filter if a DVT is found. Our next objective is to implement the CPG in TBI patients admitted to the intensive care unit and trauma services and compare rates of VTEs between historical controls and prospective patients treated in accordance with the CPG.

To our knowledge, this is the most extensive review of early VTEp administration in TBI patients, but there are several limitations of this study. For example, our meta-regression analysis did not detect a statistically significant relationship between timing of VTEp and hemorrhagic progression; however, because of study heterogeneity it is not possible to tell if the timing of VTEp truly has no influence on hemorrhagic progression or if the included studies are simply too heterogeneous to detect such an association. Additionally, most of the studies in our review did not specify which type of ICH (e.g. subarachnoid hemorrhage, epidural hematomas, subdural hematomas, contusions) were at higher risks of rebleeding following VTEp. We use TBI as an umbrella term for cerebral hemorrhage; however, in reality, TBI is a heterogeneous group of injuries with different clinical features that are likely to respond differently to VTEp. Future research could focus on clarifying what characteristics of TBI are higher risk for progression following VTEp administration. We are also critical of using radiologic criteria to determine TBI progression; for example, dichotomizing TBI radiographically as either having “progressed” or “not progressed” fails to quantify the degree of expansion and association with clinical sequelae. Future research could focus on correlating radiographic TBI progression with clinical neurologic status. Also, lack of DVT screening in many of the studies has likely caused us to underestimate the true rates of VTE. Research on the utility of weekly DVT screening in trauma patients who are not administered VTEp could be an important area of future study because the long-term sequelae of subclinical DVTs may include postthrombotic syndrome, venous stasis, and delayed rehabilitation.⁶² Last, our preliminary CPG was developed based on a combination of findings identified from this review and expert opinion from a single center. Certainly, expert opinion from a single center represents the lowest grade of evidence, and the CPG itself is meant for low hemorrhagic risk patients, which limits its generalizability. Creating protocols for VTE prevention in high hemorrhagic risk TBI patients, such as those requiring neurosurgical intervention, was beyond the scope of this review, but is an important area for potential future research.

In conclusion, we have systematically reviewed the literature to determine that it is likely safe to administer VTEp 24 hours postinjury in clinically stable patients who have sustained a low hemorrhage risk TBI that has not progressed on repeat CT scan of the head. Future research is needed to identify specific risk factors for hemorrhagic progression that may preclude early VTEp

administration. Until such factors are clearly delineated, we recommend a relatively conservative, yet consistent approach that includes administering VTEp within 24 hours of injury in patients with extra-axial hematomas smaller than 4 mm who are without coagulopathy or anticoagulant medications and have a radiographically and clinically stable TBI.

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DISCLOSURES

The authors have nothing to disclose.

STATEMENT OF AUTHORSHIP

JM: Literature search, study design, data collection, data interpretation, writing and critical revision. CD: Literature search, study design, data collection, data interpretation, critical revision. KD: Study design and critical revision. WC: Statistical analysis and critical revision. DCE: Study design and critical revision. MSS: Study design and critical revision. NG: Study design and critical revision. DEGG: Study design and critical revision. PG: Study design and critical revision. SMH: Principal investigator, study design, critical revision.

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APPENDIX

Literature Search Strategy

Literature search was performed with the assistance of the College of Physicians and Surgeons of British Columbia (CPSBC) librarian, using the CPSBC library access to EMBASE and MEDLINE databases.

Medline (Through the PubMed Interface)

“Brain Injuries/therapy”[Mesh]

AND

“Venous Thrombosis/prevention and control”[Mesh] OR

“Venous Thromboembolism/prevention and control”[Mesh] OR

“Anticoagulants”[Mesh] OR “Fibrinolytic Agents”[Mesh] AND

“Thrombolytic Therapy”[Mesh]

AND

english[lang] AND “Humans”[Mesh]

OR

“Brain Injuries”[Mesh]

AND

prophylaxis[tiab]

AND

“Venous Thrombosis/prevention and control”[Mesh] OR

“Venous Thromboembolism/prevention and control”[Mesh] OR

“Anticoagulants”[Mesh] OR “Fibrinolytic Agents”[Mesh] AND

“Thrombolytic Therapy”[Mesh]

AND
english[lang] AND "Humans"[Mesh]

Limits: 1999 +

EMBASE

exp *traumatic brain injury/dm, dt, rh, th [Disease Management, Drug Therapy, Rehabilitation, Therapy]

AND

exp venous thromboembolism/pc [Prevention] OR exp anticoagulant agent/ OR exp fibrinolytic agent/ OR exp fibrinolytic therapy/ OR (anticoagula* OR prophyla* OR chemoprophyla* OR thromboprophyla* OR antithromb*).ti,ab.

NOT

(book or book series or conference abstract or conference paper or conference proceedings or "conference review" or short survey or trade journal).pt.

NOT

exp animal/ not exp human/

⇒ NOT HELPFUL AT ALL!

Second try:

exp *traumatic brain injury/

AND

exp venous thromboembolism/pc [Prevention] OR exp anticoagulant agent/ OR exp fibrinolytic agent/ OR exp fibrinolytic therapy/ OR (anticoagula* OR prophyla* OR chemoprophyla* OR thromboprophyla* OR antithromb*).ti,ab.

NOT

(seizure prophylaxis OR preinjur* OR pre-injur*).ti,ab.

NOT

(book or book series or conference abstract or conference paper or conference proceedings or "conference review" or short survey or trade journal).pt.

NOT

exp animal/ not exp human/

⇒ much better!

Limits: English, 1999 + , remove duplicates

Search Strategies

Some syntax that were used to describe search strategies:

AND means the article must contain at least one of the terms in the line above, and at least one of the terms below, in order to appear in the search results.

OR means the article must contain at least one of the terms in order to be found. Used for synonyms e.g. Venous Thrombosis OR Venous Thromboembolism

NOT means the article must not contain any of the search terms in the line below. e.g. NOT trade journal.pt. removes any results from trade journals from the search results.

The PubMed interface to Medline uses these tags:

[Mesh] means Medical Subject Headings. These are labels placed on each article to show what the article is about. These are highly effective, as they are "exploded" – that is, a search for "Anticoagulants"[Mesh] will search for more specific types of anticoagulants, such as Antithrombin Agents.

[tiab] means a search for this word in the title and abstract of all available articles

The EMBASE database uses different syntax:

exp something/ means that this term was searched as an Emtree Subject Heading. These are labels like Medical Subject Headings, just a different set because it's a different database. The "exp" part stands for explode, and works the same way as in PubMed, for example, *exp venous thromboembolism/* includes the search *deep vein thrombosis/* automatically.

asterisk (*) between the exp and the term means that one is searching for articles where this Subject Heading is considered to be the main focus of the article – that is, most if not all of the article is about this concept. It is particularly useful in the EMBASE database to eliminate irrelevant results.

(something).ti,ab. searches for the search word in the title and abstract of all available articles

asterisk (*) means any ending for the word. E.g. anticoagula* will search for anticoagulant, anticoagulants, anticoagulation, anticoagulate, and so forth.

(something).pt. searches for particular document types. I often use this when I receive a large number of results, in order to remove items which are irrelevant (such as trade journals) and items which are hard to obtain (such as books and conference publications).

exp animal/ not exp human/ is a way of removing animal studies without removing articles about humans. Unlike Medline, EMBASE is not as consistent about labeling their Human studies, so this way removes any obviously irrelevant articles while leaving the unlabelled ones intact.

pre-injur*.ti,ab. searches for both "pre injury" and "pre-injury" automatically.

Remove duplicates is useful in the Ovid version of EMBASE (which I used), to find any articles which have been entered into the database twice, and remove the extra copies.