

## Form "EAST Multicenter Study Proposal"

<b>Study Title</b>	Safety of therapeutic anticoagulation in patients with traumatic brain injury: a multi-center prospective observational study
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<b>Co-primary investigator</b>	Stefan Leichtle  Severely injured patients are at high risk for the development of venous thromboembolism (VTE). Despite aggressive mechanical and chemical prophylaxis, the incidence of VTE in trauma patients is reported to be as high as 40% in previous literature (1). Traumatic brain injury (TBI) is associated with an even higher incidence of VTE (2). Anticoagulation therapy (ACT) with different types of anticoagulants is considered as a primary treatment for the new onset VTE (3). ACT also becomes if patients have other medical conditions requiring ACT including atrial fibrillation or mechanical heart valve (4, 5).
<b>Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined</b>	However, serious adverse events related to ACT, most importantly the progression of TBI, can be life-threatening. Care providers often face a dilemma between the risks of ACT versus thromboembolic complications in patients with TBI. Currently, a decision on initiating ACT is usually based on anecdotal experiences or expert opinions as there is scarce data regarding the safety of ACT following TBI (6). Our group conducted a single-center retrospective study which showed preliminary data regarding the safety of ACT in patients with TBI (This paper will be presented at the 29th EAST Annual Scientific Assembly) (7). We found that 8.3% of the study patients had progression of TBI on the repeat CT after ACT without neurological deterioration. Age $\geq$ 65 years was significantly associated with the progression of TBI after ACT. Hence, we sought to design a prospective study to validate our results.
<b>Primary aim</b>	To describe the current practice of ACT in TBI patients (indications, timing, type of anticoagulant) and their outcomes.  To identify factors associated with the progression of TBI in patients who received ACT.
<b>Secondary aims</b>	To compare the outcomes including the progression of TBI and thromboembolic events in patients receiving ACT to a matched cohort of patients not receiving ACT.
<b>Inclusion Criteria</b>	Patients = 18 years of age with computed tomography-proven TBI (subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage) who received anticoagulation therapy within 30 days of the initial injury (unfractionated heparin, low molecular weight heparin, Vitamin K antagonist, direct thrombin inhibitor, direct anti-Xa inhibitor, other anticoagulants)
<b>Exclusion Criteria</b>	Patients < 18 years of age, pregnancy, patients transferred from outside institutions on therapeutic anticoagulation therapy, Jail patients

**Therapeutic Interventions**

Prospective observational study only. Patients will be managed according to surgeon's discretion

and/or institutional protocol.

**Primary Outcome**

Incidence of clinically significant progression of TBI following ACT

Incidence of the progression of TBI on repeat CTs, major complications

(hemorrhagic or thromboembolic), 30- and 60-day mortality, discharge functional status

**Secondary Outcomes**

(Glasgow Outcome Scale), discharge location (home, long-term acute care facility,

rehabilitation facility, skilled nursing facility)

**List specific variables to be collected & analyzed**

Patient baseline demographics, admission physiology, injury information, imaging (type of TBI, Rotterdam score), management variables, indication for anticoagulation therapy, outcomes.

**Outline the data collection plan and statistical analysis plan succinctly**

Standard data will be collected for each patient enrolled in the study (below). Risk factors for the progression of TBI (clinical, radiographic) will be examined using univariate and multivariate analysis. We will report the mean values for parametric continuous variables and median values for non-parametric data. In univariable analyses, we will use Student-t test or Fisher's exact test for continuous variables and chi-square test or Mann-Whitney test for categorical variables as appropriate. Subsequently, multiple logistic regression models were created for each outcome adjusting for clinically significant potential confounders. We reported odds ratios (ORs) and 95% confidence intervals (CIs) for all variables.

**Outline consent procedures here, if applicable**

This is a prospective observational study. Waiver of informed consent is requested. No intervention will be performed and no change in patient management will occur as a result of this study being conducted. All data will be collected by the research personnel, in a secure database with patient identifiers, but those identifiers will be coded with and kept in a secure locker or password-protected computers.

**Succinctly outline a risk/benefit analysis**

There is scarce data regarding the safety of anticoagulation therapy in patients with traumatic brain injury. If the risk factors for the progression of TBI following anticoagulation therapy can be identified to optimize outcomes in these patients, then significant benefit will result.

1.Thorson CM, Ryan ML, Van Haren RM, Curia E, Barrera JM, Guarch GA, Busko AM, Namias N, Livingstone AS, Proctor KG. Venous thromboembolism after trauma: a never event? Crit Care Med. 2012;40:2967-73.

2.Reiff DA, Haricharan RN, Bullington NM, Griffin RL, McGwin G Jr, Rue LW 3rd. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. J Trauma. 2009;66:1436-40.

3. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA. 2014;311:717-28.

4.Whitlock RP, Sun JC, Frenes SE, Rubens FD, Teoh KH; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e531S-75S.

**Include a brief listing of  
key references**

5.Whitlock RP, Sun JC, Frenes SE, Rubens FD, Teoh KH; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e576S-600S.

6.Byrnes MC, Irwin E, Roach R, James M, Horst PK, Reicks P. Therapeutic anticoagulation can be safely accomplished in selected patients with traumatic intracranial hemorrhage. World J Emerg Surg. 2012;7:25.

7.Matsushima K, Inaba K, Cho J, Cornell C, Mohammed H, Herr K, Strumwasser A, Magee G, Grabo D, Benjamin E, Lam L, Demetriades D. Safety of therapeutic anticoagulation in patients with traumatic brain injury (abstract). 29th Eastern Association for the Surgery of Trauma Annual Scientific Assembly. San Antonio, Texas, January 13, 2016.