Title

Anticoagulation therapy in patients with traumatic brain injury: An Eastern Association for the Surgery of Trauma multicenter prospective study

Journal

Surgery, 169(2)

ISSN

0039-6060

Authors

Matsushima, Kazuhide
Leichtle, Stefan W
Wild, Jeffrey
et al.

Publication Date

2021-02-01

DOI

10.1016/j.surg.2020.07.040

Peer reviewed

HHS Public Access

Author manuscript

Surgery. Author manuscript; available in PMC 2021 August 24.

Published in final edited form as:

Surgery. 2021 February ; 169(2): 470–476. doi:10.1016/j.surg.2020.07.040.

Anticoagulation therapy in patients with traumatic brain injury: An Eastern Association for the Surgery of Trauma multicenter prospective study

Kazuhide Matsushima, MD[1], **Stefan W. Leichtle, MD**[2], **Jeffrey Wild, MD**[3], **Katelyn Young, BS**[3], **Grace Chang, MD**[4], **Demetrios Demetriades, MD, PhD**[1], **EAST ACT-TBI Multicenter Study Group**

[1:]Division of Acute Care Surgery, LAC+USC Medical Center, Los Angeles, CA

[2:]Division of Acute Care Surgical Services, VCU Medical Center, Richmond, VA

[3:]Section of Trauma and Emergency General Surgery, Geisinger Medical Center, Danville, PA

[4:]Division of Trauma and Surgical Critical Care, Mount Sinai; Division of Surgical Critical Care, University of Chicago, Chicago, IL

Abstract

Background: Trauma care providers often face a dilemma regarding anticoagulation therapy (ACT) initiation in patients with traumatic brain injury (TBI) owing to the associated risks of TBI progression. The aims of this study were 1) to describe the current practice of ACT in TBI patients and their outcomes, and 2) to identify factors associated with the progression of TBI following ACT.

Methods: In this multicenter prospective observational study, we included computed tomography-proven TBI patients who received ACT within 30 days of hospital admission. Our primary outcome was the incidence of clinically significant progression of TBI post ACT initiation.

Results: A total of 168 patients were enrolled over 22 months. Atrial fibrillation and venous thromboembolism were the most common pre- and post-injury ACT indications, respectively. Overall, 16 patients (9.6%) experienced clinically significant TBI progression following ACT, out of which 9 (5.4%) patients subsequently required neurosurgical interventions. Between patients with clinical progression of TBI and patients who showed no such progression, there were no significant differences in the baseline demographics and severity of TBI. However, ACT was initiated significantly earlier in patients of the deterioration group than those of the no-deterioration group (4.5 days vs. 11 days, p=0.015). In a multiple logistic regression model,

Corresponding Author Kazuhide Matsushima, MD, Assistant Professor of Surgery, University of Southern California, LAC+USC Medical Center, 2051 Marengo Street, Inpatient Tower (C), C5L100, Los Angeles, CA 90033, Tel: 323-409-8597, Fax: 323-441-9907, kazuhide.matsushima@med.usc.edu.

All authors deny any potential conflicts of interest

All authors attest that they fulfill the COPE (Committee on Publication Ethics) requirement for authorship

This paper was presented at the 32nd Annual Scientific Assembly of the Eastern Association for the Surgery of Trauma, January 17, 2019 Austin, Texas (Oral plenary)

patients who received ACT later after injury had significantly lower risk of clinically significant TBI progression (odds ratio: 0.915 for each day, 95% confidence interval: 0.841-0.995, p=0.037).

Conclusions: Our results suggest that early ACT is associated with higher risk of TBI progression, thus a balance between bleeding and thromboembolic risks should be carefully evaluated in each case before initiating ACT.

Keywords

traumatic brain injury; anticoagulation therapy; outcome

Introduction

Anticoagulation therapy (ACT) is considered the primary treatment for venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism.[1] ACT is also indicated for patients with medical conditions, such as atrial fibrillation (AF), that are associated with thromboembolic complications and for those with mechanical heart valves.[2, 3] Previous studies have shown significant outcome benefits in patients with these conditions treated with ACT despite the associated risk of bleeding complications.[4-6] As a result, an increasing number of patients currently receive ACT for various indications.[7]

Severely injured trauma patients are at a high risk for development of VTE. Despite aggressive mechanical and chemical prophylaxis, the incidence of VTE in such patients is reported to be as high as 40%.[8] Patients with traumatic brain injury (TBI) are at particularly high risk for VTE.[9] In addition, the number of trauma patients who are on ACT for a pre-existing medical condition is expected to increase as the population ages.[10]

However, adverse events associated with ACT, most importantly the progression of hemorrhagic TBI, can be catastrophic and life-threatening. Consequently, trauma care providers often face a dilemma regarding ACT initiation in the setting of TBI owing to both the major bleeding risks of ACT and the thromboembolic complications associated with a recent TBI. Currently, the decision on ACT initiation is often based on expert opinions as only scarce data are available regarding the safety of ACT following a TBI.[11-14] Therefore, we sought to: 1) describe the current practice of ACT in TBI patients and associated outcomes, and 2) identify factors associated with TBI progression following initiation of ACT. We hypothesized that earlier initiation of ACT would be associated with increased risk for clinically significant TBI progression.

Methods

Study design and patient selection

This was a prospective, multicenter, observational study sponsored by the Eastern Association for the Surgery of Trauma (EAST) Multicenter Trial Committee. The Institutional Review Board (IRB) at the University of Southern California as the coordinating center approved this study. Subsequently, this study was approved by the IRBs at the other 15 participating centers. A waiver of informed consent was granted by the IRB due to the observational nature of this research. From April 2016 to January

2018, patients who sustained computed tomography (CT)-proven hemorrhagic TBI (epidural hematoma, subdural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage) and received ACT during hospital stay within 30 days of injury were selected for the study. Anticoagulants administered during the ACT included unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonist (VKA), direct thrombin inhibitor, and direct factor Xa inhibitor. No standardized protocol was used for TBI management in the selected patients, and ACT was initiated at the discretion of clinicians and/or as per the institutional guidelines. Patients under the age of 18 years, prisoners, pregnant patients, and transferred patients who were already on ACT were excluded from the study.

Data collection and Statistical analysis

The following variables were collected at each participating center: patient baseline demographics, admission physiology, severity of injuries, head CT findings, the Rotterdam score, TBI management parameters (intracranial pressure monitoring, surgical interventions including craniotomy and craniectomy), ACT parameters (indications, type, and timing), and patient outcomes.[15] All the data from the coordinating center and the other participating centers were collected through REDCap (Research Electronic Data Capture), a secure on-line data entry and management system. The primary outcome was the incidence of clinically significant deterioration of TBI following initiation of ACT characterized by either, 1) a decrease in Glasgow Coma Scale (GCS) >2 points, 2) transfer to higher level of care, or 3) need for neurosurgical intervention. Other outcomes of interest included the incidence of radiographic progression of TBI as determined by repeat head CT following initiation of ACT. In addition, other hemorrhagic complications resulting in transfusion requirement, radiological interventions, or other surgical interventions, as well as in-hospital mortality, discharge functional status (Glasgow Outcome Scale), and discharge location were collected.

Our study cohorts were divided into two groups, namely, the clinical deterioration group and the no-deterioration group. Clinical factors associated with clinical progression of TBI and patient outcomes were compared using univariate and multivariate analyses. In univariate analyses, we used Student’s t-test or Mann-Whitney U test for continuous variables, and chi-square test or Fisher’s exact test for categorical variables as appropriate. Subsequently, multiple logistic regression analysis was performed for clinical progression of TBI following initiation of ACT, adjusting for clinically significant potential confounders. We reported odds ratios (OR) and 95% confidence intervals (CI) for each covariate. A p-value < 0.05 was considered significant. Our sample size estimates were based on the previous retrospective study given the lack of prospective studies.[12] We assumed that the incidence of clinically significant TBI progression would be up to 5%. Thus, for this prospective observational study, we anticipated requiring 126 TBI patients who receive ACT (confidence level: 99%, expected proportion: 0.05, total width pf the confidence interval: 0.1). All statistical analyses were performed using STATA 13.0 (StataCorp LP, College Station, Texas).

Results

During the 22-month study period, a total of 168 patients from 16 centers met our inclusion criteria. Due to missing data for one of the patients, 167 patients were included for the analysis, (Figure 1). The median age was 62 years (inter quartile range, IQR: 43-75) and 68.5% of them were male. The median time for ACT was 10 days (IQR: 5-17 days). Clinical signs of neurological deterioration were observed in 16 patients (9.6%) following initiation of ACT and the median number of days from the ACT initiation to clinical deterioration was 3 days (IQR: 2-6 days). Patient characteristics and injury severity were compared between the clinical deterioration group and the no-deterioration group (Table 1). There was no significant difference between the two groups with respect to basic demographics, including comorbid medical conditions. However, while less than 50% of patients in the no-deterioration group were >65 years-old, 68.8% of patients in the clinical deterioration group were >65 years-old (p=0.063). The majority of the patients included in the study were admitted following blunt trauma, and subdural hematoma was the most common type of TBI. The severity of TBI (radiographic and clinical signs) was similar between the two study groups. Neurosurgical interventions were performed within 24 hours after admission in 36% of patients, distributed evenly between both study groups.

ACT was indicated for various pre- and post-injury comorbid conditions (Table 2). AF was the most common pre-injury indication while VTE was the most common post-injury indication. ACT was initiated significantly earlier in the clinical deterioration group than in the no-deterioration group (4.5 days vs. 11.0 days, p=0.015). UFH infusion was the most commonly used agent for ACT, followed by LMWH. Direct oral anticoagulants (DOACs: direct factor Xa inhibitor and direct thrombin inhibitor) were used in only 16 patients, all of whom were in the no-deterioration group (10.6%).

Of 151 patients in the no-deterioration group, 9 patients showed radiographic progression of TBI on repeat head CT (6.0%) (Table 3). No additional invasive procedures were required in these patients, but ACT was discontinued in 6 patients (66.7%). Of 16 patients with clinical deterioration, 9 patients (56.3%) required further invasive procedures (6 intracranial pressure monitoring, 2 craniectomy, 1 burr hole drainage). GCS was decreased >2 points in 14 patients (87.5%) and 8 patients (50.0%) required transfer to the intensive care unit.

A total of 11 patients (5 in the clinical deterioration group and 6 in the no-deterioration group) developed other hemorrhagic complications on ACT including airway and gastrointestinal bleeding, retroperitoneal hematoma, and wound-related hemorrhage. Of those, 6 patients required surgical, endovascular, or endoscopic interventions for hemorrhage control. In-hospital mortality was significantly higher in the clinical deterioration group than the no-deterioration group (37.5% vs. 3.3%, p<0.001). Similarly, functional outcomes upon discharge were significantly worse in the clinical deterioration group than the no-deterioration group. In a multiple logistic regression model for analysis of clinical deterioration following ACT, the following covariates were adjusted: age (>65 years), days from injury to ACT, and the Rotterdam CT score (Table 4). Patients who had ACT initiated after a greater number of days following injury showed significantly lower risk of clinical deterioration (OR: 0.915 for each day, p=0.037).

Discussion

The determination to initiate ACT following TBI is difficult with unknown risks to ideally counsel patients. In this prospective multicenter study, the largest to date, we observed that approximately 10% of TBI patients developed neurologic deterioration following the initiation of ACT. While patient demographics and TBI severity were similar between the patients of the clinical deterioration group and the no-deterioration group, earlier initiation of ACT was significantly associated with an increased risk of clinical deterioration. These results suggest that early initiation of ACT in patients with TBI confers a significant risk of adverse outcomes. Therefore, the indications for ACT should be carefully evaluated in each patient and the timing of the ACT should be determined on the basis of associated risks and benefits. Once ACT is initiated, the neurologic status of the patient needs be monitored closely for any signs of neurologic deterioration.

While safety and efficacy of chemical thromboprophylaxis following a TBI have been extensively studied in the past decade, little is known regarding the safety of its therapeutic use following TBI.[16] Pandya et al. conducted a retrospective single-center study to describe the outcome of patients who received antithrombotic therapy, including ACT and antiplatelet therapy.[13] They reported development of clinically significant expansion of TBI in one patient out of the 35 patients who were only given ACT (2.9%) and in another patient out of the 11 patients who were give both ACT and antiplatelet therapy (9.1%). This low incidence of complications associated with ACT in TBI patients was also suggested in other single-center studies.[11, 12, 14] In a retrospective study including 26 TBI patients who received ACT, Byrnes et al. observed only one patient (3.8%) with minor expansion of intraparenchymal hemorrhage as revealed by a follow-up head CT.[11] The average time from injury to ACT was 11.9 days and notably, two patients were anticoagulated within 24 hours of injury without any hemorrhagic complications. Shahan et al. reviewed 93 TBI patients who underwent antithrombotic therapy for associated blunt cerebrovascular injury (BCVI).[14] They used low-intensity heparin infusion (goal activated partial thromboplastin time: 45-60 seconds) and none of the 93 TBI patients developed clinical deterioration; however, 9% of them were found to have expansion of TBI on repeat imaging. Another single-center study including 72 TBI patients also showed that 8.3% of TBI patients on ACT developed hemorrhagic TBI, as demonstrated by repeat head CT.[12] However, none of them developed any signs of neurologic deterioration.

In contrast to prior studies, 9.6% of our study patients developed clinically significant neurologic deterioration after ACT initiation post TBI. Of those, 56.3% required further surgical interventions for the control of TBI progression. Overall, in-hospital mortality rate and functional outcomes upon discharge were significantly worse in the clinical deterioration group than the no-deterioration group. The median time to ACT in the clinical deterioration group was 4.5 days (IQR: 2.5-12 days), but there were also four patients for whom ACT was initiated after 12 days following injury (13, 13, 17, 26 days). Although the heterogeneity between each study makes comparisons challenging, the results in our study suggest that the use of ACT is not always safe in patients with a recent TBI. Thus, clinicians should take in account all the associated risks and benefits of ACT for each case. In particular, patients should always be evaluated for their comorbid conditions before ACT

administration. For example, the risk of thromboembolic complications for patients with a mechanical mitral valve would be different from patients with AF and a low CHA_2DS_2-VAS_c score.[17, 18] In a recent randomized trial, forgoing perioperative bridging ACT was found to be non-inferior to LMWH bridging for preventing arterial thromboembolism in AF patients undergoing elective surgery.[19]

The second aim of this study was to identify clinical factors associated with risk of clinically significant neurologic deterioration after initiation of ACT. In a previous retrospective study, multiple logistic regression analysis was performed to identify significant predictors of hemorrhagic expansion following ACT with the help of repeat head CT.[12] Age over 65 years was found to be a significant predictor, whereas the Rotterdam score on initial CT, and the timing of ACT (<10 days after injury) were not significantly associated with expansion of hemorrhagic TBI. Another retrospective study suggested that SDH is a significant risk factor associated with hemorrhagic expansion post antithrombotic therapy.[13] However, our multivariate analysis found that age (>65 years) and the Rotterdam score on initial CT were not significantly associated with clinical deterioration post ACT. Instead, the timing of ACT appeared to be the most important risk factor for clinical deterioration. While we were not able to provide specific recommendations for the timing of ACT initiation due to a relatively small sample size, the duration between injury and the initiation of ACT should be the major driving factor in discussions with the patient regarding the risk of TBI progression.

There are several important limitations to our study. First, owing to the observational nature of the study, the decision to initiate ACT was made based on clinical judgment. Consequently, there might be significant variations in selecting patients who received ACT between each participating center. As we did not include a group of patients for whom ACT was indicated but not initiated during their hospital stay, thromboembolic risks in those patients remain unknown. Similarly, the decisions on obtaining the pre- and post-ACT head CTs to evaluate the progression of TBI were made on clinicians' discretion. Therefore, withholding ACT based on radiographic progression of TBI on a repeat CT might have prevented clinical progression for patients in the no-deterioration group. Second, the definition of clinically significant progression of TBI in our study can be subjective. For example, we did not implement a universal protocol for determining surgical indications in patients with worsening TBI. Third, the type of anticoagulant that should be considered for the first-line treatment in the patients with a recent TBI remains unknown. In the meantime, clinicians should be familiar with the pros and cons of commonly used anticoagulants.[20] Our results suggest that DOACs might be safe to be used in patients with recent TBI (0/10 patients developed clinically significant progression of TBI). While previous retrospective studies showed improved clinical outcomes related to the pre-injury use of DOACs compared with VKA in patients with TBI, further prospective studies with a larger sample size are still required.[21, 22] Finally, we were not able to determine the long-term risk of hemorrhagic complications post ACT in TBI patients. In a retrospective cohort study using the administrative database in Denmark, resumption of warfarin therapy for AF in TBI patients was significantly associated with a lower relative risk of death in one year following their discharge.[23] Interestingly, resuming warfarin therapy in TBI patients was also associated with a lower rate of recurrent intracranial hemorrhage.

Conclusions

Patients with recent TBI who require ACT for indicated conditions need to be carefully evaluated to determine both their risk for progression of TBI and thromboembolic complications. The results of our study suggest that earlier initiation of ACT is associated with increased risk of clinically significant TBI progression. Therefore, the timing of ACT initiation should be tailored for each case based upon this risk and the risk for thromboembolic complications without ACT.

Acknowledgement

The authors would like to thank Monica Wong for the technical support in conducting this multicenter prospective study.

Neither internal nor external financial support was used for this study

Appendix

* The EAST ACT-TBI Multicenter Study Group

Cara Diaz Lomangino, ACNP (cdiaz@umm.edu)

Jennifer Massetti, ACNP (jmassetti@umm.edu)

R Adams Cowley Shock Trauma center, University of Maryland Medical Center, Baltimore, MD

Nina E. Glass, MD (ng470@njms.rutgers.edu)

David H. Livingston, MD (livingst@nims.rutgers.edu)

Division of Trauma and Acute Care Surgery, Rutgers-New Jersey Medical School. Newark, NJ

Karen O'Bosky, MD (kobosky@llu.edu)

Julie L. Chan, MD, PhD (Julie.chan@cshs.org)

Division of Trauma/Acute Care, Loma Linda University Medical Center, Loma Linda, CA

Daniel C. Cullinane, MD (cullinane.daniel@marshfieldclinic.org)

Department of Surgery, Marshfield Clinic, Marshfield, WI

Kelly A. Rippey, MD (krippey@hackensackumc.org)

Jyoti Sharma, MD (jsharma@hackensackumc.org)

Division of Trauma, Surgical Critical Care and Injury Prevention, Hackensack University Medical Center, Hackensack, NJ

Jeffry Nahmias, MD, MHPE (jnahmias@uci.edu)

Areg Grigorian, MD (agrigori@uci.edu)

Division of Trauma, Burns and Surgical Critical Care, University of California, Irvine, Orange, CA

Steven Allen, MD (sallen@pennstatehealth.psu.edu)

Scott B. Armen, MD (sarmen@pennstatehealth.psu.edu)

Division of Trauma, Acute Care & Critical Care Surgery, Penn State Hershey Medical Center, Hershey, PA

John D. Berne, MD (jberne@aol.com)

Dalier Mederos, MD (drodriguezmederos@browardhealth.org)

Division of Trauma and Critical Care, Broward Health Medical Center, Fort Lauderdale, FL

Jose L. Pascual, MD, PhD (jose.pascual@uphs.upenn.edu)

Division of Trauma & Surgical Critical Care, University of Pennsylvania, Philadelphia, PA

Shelby Resnick, MD (Shelby.resnick@gmail.com)

Department of Trauma Surgery, Kaiser Permanente-South Sacramento, Sacramento, CA

Omar Bholat, MD (obholat@northwell.edu)

Lauren Ostry, MD (lauren.ostry@gmail.com)

Division of Acute Care Surgery, North Shore University Hospital, Manhasset, NY

Luis J. Garcia, MD (luis-garcia@uiowa.edu)

Rafael Ramos Vecchio, MD (rafaelalejandro-ramosvecchio@uiowa.edu)

Division of Acute Care Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA

Eleanor S. Winston, MD (Eleanor.winston@baystatehealth.org)

Division of Trauma and Acute Care Surgery, Baystate Medical Center, Springfield, MA

Andrew F. Sabour, MD (asabour@usc.edu)

Division of Acute Care Surgery, LAC+USC Medical Center, Los Angeles, CA

References

1. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA. 2014;311:717–28. [PubMed: 24549552]

2. Lip GYH, Banerjee A, Boriani G, et al.Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154:1121–1201. [PubMed: 30144419]
3. Whitlock RP, Sun JC, Fremes SE, et al.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. [PubMed: 22315272]
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67. [PubMed: 17577005]
5. Schulman S, Kearon C, Kakkar AK, et al.Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342–52. [PubMed: 19966341]
6. Patel MR, Mahaffey KW, Garg J, et al.Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91. [PubMed: 21830957]
7. Barnes GD, Lucas E, Alexander GC, et al.National trends in ambulatory oral anticoagulant use. Am J Med. 2015;128:1300–5. [PubMed: 26144101]
8. Thorson CM, Ryan ML, Van Haren RM, et al.Venous thromboembolism after trauma: a never event?Crit Care Med. 2012;40:2967–73. [PubMed: 22890248]
9. Reiff DA, Haricharan RN, Bullington NM, et al.Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. J Trauma. 2009;66:1436–40. [PubMed: 19430251]
10. Maung AA, Bhattacharya B, Schuster KM, et al.Trauma patients on new oral anticoagulation agents have lower mortality than those on warfarin. J Trauma Acute Care Surg. 2016;81:652–7. [PubMed: 27438683]
11. Byrnes MC, Irwin E, Roach R, et al.Therapeutic anticoagulation can be safely accomplished in selected patients with traumatic intracranial hemorrhage. World J Emerg Surg. 2012;7:25. [PubMed: 22824193]
12. Matsushima K, Inaba K, Cho J, et al.Therapeutic anticoagulation in patients with traumatic brain injury. J Surg Res. 2016;205:186–91. [PubMed: 27621017]
13. Pandya U, Pattison J, Karas C, et al.Does the presence of subdural hemorrhage increase the risk of intracranial hemorrhage expansion after the initiation of antithrombotic medication?Am Surg. 2018;84:416–421. [PubMed: 29559058]
14. Shahan CP, Magnotti LJ, McBeth PB, et al.Early antithrombotic therapy is safe and effective in patients with blunt cerebrovascular injury and solid organ injury or traumatic brain injury. J Trauma Acute Care Surg. 2016;81:173–7. [PubMed: 27027559]
15. Deepika A, Prabhuraj AR, Saikia A, et al.Comparison of predictability of Marshall and Rotterdam CT scan scoring system in determining early mortality after traumatic brain injury. Acta Neurochir (Wien). 2015;157:2033–8. [PubMed: 26374440]
16. The American College of Surgeons Trauma Quality Improvement Program. Best practices in the management of traumatic brain injury. https://www.facs.org/quality-programs/trauma/tqp/center-programs/tqip/best-practice.Accessed November 13, 2018.
17. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89:635–41. [PubMed: 8313552]
18. Lip GY, Nieuwlaat R, Pisters R, et al.Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263–72. [PubMed: 19762550]
19. Douketis JD, Spyropoulos AC, Kaatz S, et al.Preoperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373:823–33. [PubMed: 26095867]
20. Hornor MA, Duane TM, Ehlers AP, et al.American College of Surgeons' guidelines for the perioperative management of antithrombotic medication. J Am Coll Surg. 2018;227:521–536. [PubMed: 30145286]
21. Shin SS, Marsh EB, Ali H, et al.Comparison of traumatic intracranial hemorrhage expansion and outcomes among patients on direct oral anticoagulants versus vitamin k antagonists. Neurocrit Care. 2020;32:407–418. [PubMed: 32034657]

22. Prexl O, Bruckbauer M, Voelckel W, et al.The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med. 2018;26:20. [PubMed: 29580268]

23. Nielsen PB, Larsen TB, Skjøth F, et al.Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. JAMA Intern Med. 2017;177:563–570. [PubMed: 28241151]

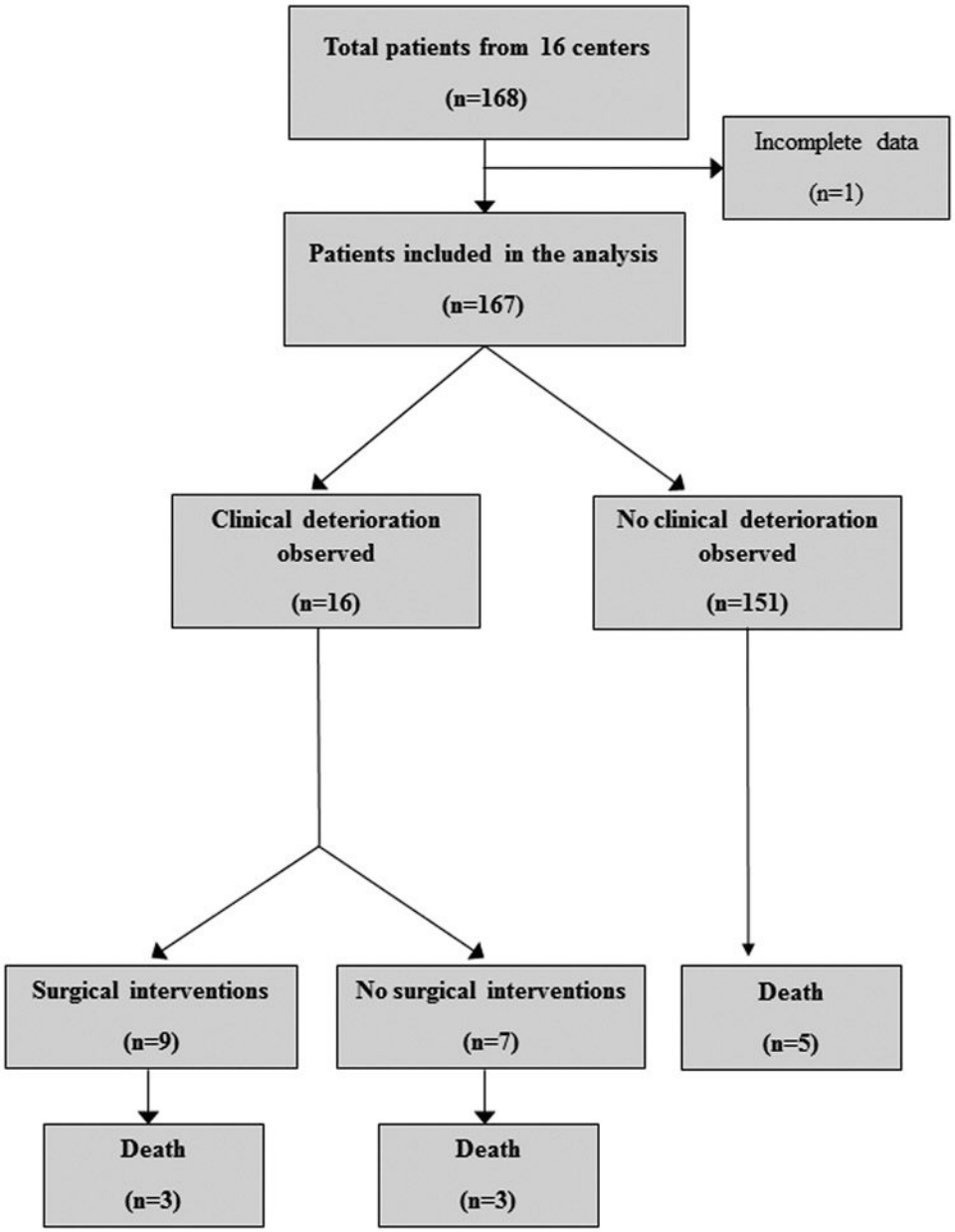

Figure 1.
Patient flow diagram

Table 1.

Patient characteristics and injury severity

Variables	No deterioration group (n=151)	Clinical deterioration group (n=16)	p value
Median age (IQR)	60 (42-74)	68.5 (41-74.5)	0.399
Age >65 years (%)	64 (42.38%)	11 (68.75%)	0.063
Sex (male)	104 (68.87%)	10 (62.50%)	0.584
Mean Body Mass Index (SD)	27.6 (0.50)	31.7 (2.17)	0.088
Comorbid conditions (%)			
Coronary artery disease	44 (29.14)	4 (25.00)	1.000
Congestive heart failure	16 (10.60)	3 (18.75)	0.398
Diabetes mellitus	27 (17.88)	4 (25.00)	0.502
COPD	7 (4.64)	3 (18.75)	0.057
Liver cirrhosis	3 (1.99)	0 (0.00)	1.000
ESRD	2 (1.32)	0 (0.00)	1.000
Mechanism of injury (%)			0.751
Motor vehicle accident	33 (21.85)	2 (12.50)	
Motor cycle accident	9 (5.96)	2 (12.50)	
Auto versus pedestrian	25 (16.56)	2 (12.50)	
Blunt assault	3 (1.99)	0 (0.00)	
Fall	68 (45.03)	8 (50.00)	
Gunshot wound	3 (1.99)	0 (0.00)	
Stab wound	1 (0.66)	0 (0.00)	
Others	9 (5.96)	2 (12.50)	
mGCS on admission (%)			0.561
1	18 (11.92)	2 (12.50)	
2	3 (1.99)	0 (0.00)	
3	7 (4.64)	0 (0.00)	
4	16 (10.60)	0 (0.00)	
5	18 (11.92)	4 (25.00)	
6	89 (58.94)	10 (62.50)	
Types of TBI (%)			
Epidural hematoma	14 (9.27)	2 (12.50)	0.654
Subdural hematoma	94 (62.25)	13 (81.25)	0.174
Subarachnoid hemorrhage	93 (61.59)	9 (56.25)	0.789
Intraparenchymal hemorrhage	34 (22.52)	4 (25.00)	0.762
Others	11 (7.28)	1 (6.25)	1.000
AIS head (%)			0.841
1	9 (5.96)	2 (12.50)	
2	26 (17.22)	2 (12.50)	
3	34 (22.52)	4 (25.00)	
4	44 (29.14)	4 (25.00)	
5	38 (25.17)	4 (25.00)	

Variables	No deterioration group (n=151)	Clinical deterioration group (n=16)	p value
Median ISS (IQR)	24 (16-33)	21.5 (15-26.5)	0.451
CT findings on admission			
Midline shift >5mm (%)	29 (19.21)	2 (12.50)	0.739
Rotterdam CT score (%)			0.781
1	37 (24.50)	5 (31.25)	
2	55 (36.42)	6 (37.50)	
3	36 (23.84)	2 (12.50)	
4	18 (11.92)	3 (18.75)	
5	4 (2.65)	0 (0.00)	
6	1 (0.66)	0 (0.00)	
Neurosurgical interventions < 24 hours after admission (%)			
External ventricular drainage	19 (12.58)	1 (6.25)	0.696
Bolt	9 (5.96)	3 (18.75)	0.093
Craniotomy	20 (13.25)	1 (6.25)	0.696
Craniectomy	17 (11.26)	2 (12.50)	1.000
None	96 (63.58)	11 (68.75)	0.789

IQR: interquartile range, COPD: chronic obstructive pulmonary disease, ESRD: end-stage renal disease, mGCS: Glasgow Coma Scale (motor), TBI: traumatic brain injury, AIS: abbreviated injury scale, ISS: injury severity score, CT: computed tomography

Table 2.

Anticoagulation therapy

Variables	No deterioration group (n=151)	Clinical deterioration group (n=16)	p value
Pre-injury ACT indications (%)			
Atrial fibrillation	31 (20.53)	3 (18.75)	1.000
Deep venous thrombosis	9 (5.96)	1 (6.25)	1.000
Pulmonary embolism	12 (7.95)	0 (0)	0.608
Mechanical heart valve	19 (12.58)	4 (25.00)	0.242
Others	12 (7.95)	1 (6.25)	1.000
Post-injury ACT indications (%)			
Atrial fibrillation	30 (19.87)	5 (31.25)	0.332
Deep venous thrombosis	61 (40.40)	8 (50.00)	0.595
Pulmonary embolism	39 (25.83)	2 (12.50)	0.362
Mechanical heart valve	19 (12.58)	3 (18.75)	0.446
Others	36 (23.84)	3 (18.75)	0.766
Median days to ACT (IQR)	11 (5-18)	4.5 (2.5-12)	0.015
Patient location upon initiation of ACT (%)			0.017
ICU	81 (53.64)	14 (87.50)	
Monitored unit (stepdown, telemetry)	33 (21.85)	2 (12.50)	
General ward	37 (24.50)	0 (0)	
Stable TBI on head CT before ACT (%)	121 (80.13)	12 (75.00)	0.744
Types of ACT (%)			0.275
Unfractionated heparin infusion	68 (45.03)	12 (75.00)	
LMWH	27 (17.88)	3 (18.75)	
Vitamin K antagonist	35 (23.18)	1 (6.25)	
Direct factor Xa inhibitor	15 (9.93)	0 (0)	
Direct thrombin inhibitor	1 (0.66)	0 (0)	
Others	5 (3.31)	0 (0)	
Supratherapeutic aPTT or PT-INR (%) *	29 (27.36)	4 (30.77)	0.753
Simultaneous antiplatelet therapy (%)	29 (19.21)	5 (31.25)	0.324

* ≥1 incident(s) of aPTT or PT-INR value twice as high as the target range

ACT: anticoagulation therapy, IQR: interquartile range, ICU: intensive care unit, CT: computed tomography, LMWH: low-molecular weight heparin, aPTT: activated partial thromboplastin time, PT-INR: prothrombin time-international normalized ratio

Table 3.

Patient outcomes

Variables	No deterioration group (n=151)	Clinical deterioration group (n=16)	p value
Radiographic progression of TBI (%)			<0.001
Yes	9 (5.96)	10 (62.50)	
No	93 (61.59)	3 (18.75)	
No repeat CT imaging	49 (32.45)	3 (18.75)	
Median days from ACT to radiographic progression (IQR)	2 (2-6)	2.5 (1-5)	0.617
ACT discontinuation (%)	6/9 (66.67)	12/16 (75.00)	0.673
Invasive interventions for progression of TBI (%)	0 (0.00)	9 (56.25)	0.008
Other hemorrhagic complications (%)	6 (3.97)	5 (31.25)	0.001
In-hospital mortality (%)	5 (3.31)	6 (37.50)	<0.001
Median length of ICU stay (IQR)	11.5 (2-23)	15 (11-21)	0.114
Median length of hospital stay (IQR)	21 (9-34)	21 (15-31)	0.535
Discharge disposition (%)			0.066
Home or back to prior living situation	42 (28.77)	0 (0.00)	
Rehabilitation facility	61 (41.78)	3 (33.33)	
Nursing home or long-term care facility	40 (27.40)	6 (66.67)	
Others	3 (2.05)	0 (0.00)	
Glasgow Outcome Scale (%)			<0.001
1	5 (3.31)	6 (37.50)	
2	8 (5.30)	0 (0.00)	
3	48 (31.79)	9 (56.25)	
4	31 (20.53)	1 (6.25)	
5	59 (39.07)	0 (0.00)	

TBI: traumatic brain injury, CT: computed tomography, ACT: anticoagulation therapy, IQR: interquatile range, ICU: intensive care unit

Table 4.

Multiple logistic regression for clinically significant deterioration

Variables	Odds ratio	95% confidence interval	p value
Age >65 years	2.892	0.917-9.123	0.070
Days from injury to ACT (1-day increment)	0.915	0.841-0.995	0.037
Rotterdam CT score >3	2.450	0.570-10.527	0.228

Hosmer-Lemeshow Goodness-of-Fit Test: p=0.59

ACT: anticoagulation therapy, CT: computed tomography