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TITLE: The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

PRINCIPAL INVESTIGATOR: Mary Margaret Knudson, MD

CONTRACTING ORGANIZATION: National Trauma Institute d/b/a Coalition for National Trauma Research

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14. ABSTRACT Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. All sites completed enrollment of participants except when restricted due to COVID-19 in CLOTT Part 1 and Part 2. Due to COVID-19, CLOTT Part 2 sites required additional time to meet enrollment targets. A 12-month extension without funds was approved. In Year 4, all CLOTT sites (17) initiated notices to their local IRBs that the federal funding was ending so that protocols can be closed with HRPO (underway). Sites completed data collection and cleaning. The first paper on CLOTT Part 1 was published in December 2021. Part 2 findings were be presented and submitted for publication in Spring 2022.					
15. SUBJECT TERMS Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shut down, clot lysis, surveillance bias					
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FINAL REPORT

1. INTRODUCTION

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. However, due to the liberal use of computed tomography following injury, many patients are found to have small clots in the chest that may not be PE at all and may in fact not need to be treated. Additionally, recent laboratory investigations suggest that some severely injured patients develop a hypercoagulable state due to failure to break down clot once formed and that platelets contribute to the strength of the clot. This failure of clot lysis may set the stage for true PE events. For Aim 1, patients aged 18-40 years who are admitted to any of 17 major trauma centers were considered eligible for enrollment. Data are collected on all patients who develop PE in order to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. The safety of observing patients with peripheral thrombi versus treatment (full-dose anticoagulation or placement of a vena cava filter) will be compared. All 17 sites closed enrollment into CLOTT 1 as planned on September 29, 2020. For Aim 2, five trauma centers enrolled a cohort of patients admitted to their intensive care unit and collect blood samples that can be subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown). The association between fibrinolytic shutdown and the subsequent development of PE was explored. Four of these sites continued enrolling during the second 12-month no-cost extension period (9/30/20 - 9/29/21). All CLOTT 2 sites closed enrollment as of the end of Year 4.

2. KEY WORDS

Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shutdown, clot lysis, surveillance bias

3. ACCOMPLISHMENTS

- What were the major goals of the project?

CLOTT 1:

Hypothesis 1: Isolated pulmonary clots detected on CT scans of the chest after injury are primary clots (PT) and not embolic.

Hypothesis 2: Risk factors for PT are different than those for traditional VTE.

Hypothesis 3: Asymptomatic PT can be simply observed without treatment.

Study Specific Aims CLOTT 1: (1) To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots (PT) discovered on computed tomography (CTA)

(2) To identify risk factors for the development of PT versus pulmonary emboli (PE).

Study Design: This study was designed as a pragmatic, prospective, multi-center, observational trial that was conducted at 17 level 1 trauma centers across the country. All injured civilian adult patients in the age range of 18-40 years (combat compatible ages) who entered one of the 17 trauma centers in the CLOTT Study group were considered eligible for enrollment if they had at least one of several previously identified post-traumatic risk factors for the development of VTE including the following: shock on admission, the presence of major head, chest or abdominal injuries, a venous injury requiring repair/ligation, a pelvic or long bone lower extremity fracture, spinal cord injury, coagulopathy on admission, or required a major operative procedure on the first day of hospitalization. All clinical research coordinators at the 17 sites were trained on the use of a specifically designed case report form (CRF) prior to the start of the study. The CRF captured demographic characteristics, trauma associated and pre-existing VTE risk factors, admission vital signs and laboratory data, mechanism of injury, blood products and procoagulants administered during the first 24 hours, Abbreviated Injury Scale and Injury Severity Scale score, length of stay, days in the intensive care unit, days receiving ventilatory support, discharge disposition, and cause of any deaths. Extensive data were collected on VTE prophylaxis used including when it was initiated, chemical prophylactic drugs ordered, missed doses (including reasons drugs were held), and any complications associated with prophylaxis. The primary outcome of interest was the presence of any clot seen on computed tomography. Data were also collected on the dates and the outcomes of all DVT duplex scans and CT scans of the chest as well as the reasons for obtaining those scans. The CRF allowed documentation of the management (treatment versus observation) of any clots (i.e., PE or PT) detected by chest CTA. Completed data forms were uploaded into a database located at the University of California San Francisco called REDCap (Research Electronic Data Capture). There was no attempt to change practice at any center during this observational study. In particular, the treatment of any clots seen on imaging was left to the discretion of the treating physician. Patients were followed until discharge or for up to 30 days in the hospital.

Accomplishments for CLOTT 1: During this study, several major goals were accomplished:

Goal 1: The extensive data collected with the CRFs were programmed into exportable files by a programmer hired at UCSF.

Goal 2: The data were analyzed by the UCSF Department of Surgery Biostatistical Group.

Goal 3: A manuscript was prepared and published in JAMA Surgery.

Results: A total of 7880 patients were included in the study, 277 with DVT, 40 with PE and 117 with isolated PT. Risk factors independently associated with PT but not DVT or PE included: shock on admission and major chest injury. PT was present on the admitting scan in 25% of patients with PT and was associated with chest injury and venous injury.

Conclusions: This is the largest prospective investigation in the world that focuses on posttraumatic PT. The study suggests that most pulmonary clots are not embolic but rather result from inflammation, endothelial injury, and the hypercoagulable state caused by the injury itself. Based on our study, we offer an algorithm for the treatment of asymptomatic PT. These findings have major implications for the treatment of isolated, asymptomatic PT in both civilian and military settings.

CLOTT 2:

Main Hypothesis: Fibrinolytic shutdown after injury will be detected frequently in critically injured patients.

Secondary Hypothesis: Fibrinolytic shutdown is associated with an increased incidence of VTE after injury.

Sub-Aim 1: To describe the incidence of and the timing for the development of fibrinolytic shutdown in critically injured patients

Sub-Aim 2: To identify the risk factors for the development of fibrinolytic shutdown after injury

Sub-Aim 3: To investigate the association between fibrinolytic shutdown and the development of DVT and/or PE

Study Design: This study included a sub-set of patients in CLOTT-1 who were admitted to one of the five CLOTT trauma centers with active coagulation research laboratories and who were severely injured requiring ICU care. In order to identify those patients who develop fibrinolytic shutdown, blood samples were drawn at the following intervals post-injury: 6, 12, 24, 36 and 48 hours and again on days 4 and 7 for thromboelastography testing (TEG), (although there was no change in management as the result of this TEG testing). Shutdown (SD) was defined as an Ly30 of $\leq 0.3\%$ on kaolin TEG assays. In order to detect severe shutdown defined as tissue plasminogen activator resistance (tPA-R) a paired sample at the same time intervals as above were subjected to tPA TEG assays with tPA-R defined as kaolin TEG with tPA 75ng Ly30% $<2.1\%$. In order to detect the association between SD and/or tPA-R and the development of VTE a duplex venous examination (ankle to groin bilaterally) was obtained on ICU day 3 unless the patient already had clot visualized on CT scans. The treatment of any clot seen was left to the discretion of the treating physician. The same data collection form (CRF) was used for CLOTT-2 as for CLOTT-1 with additional TEG data added for CLOTT-2.

Accomplishments during this period for CLOTT 2

Goal 1: The data from subgroup of patients enrolled in CLOTT-2 with paired samples available for the first 12 and 24 hours were analyzed for both SD and tPA-R.

Goal 2: The risk factors for the development of SD and tPA-R were analyzed.

Goal 3: An abstract was accepted and presented at the Western Trauma Association annual meeting (February 20-25, 2022) and the corresponding manuscript was submitted to The Journal of Trauma and Acute Care Surgery.

Results: 141 patients had both TEG measurements at 24 hours and 135 had both at 12 hours. SD was evident at 12 hours in 52.6% of patients and in 44% at 24 hours. tPA-R was found in 45.2% of patients at 12 hours and in 34.3% at 24 hours. Factors significantly associated with SD include receiving > 4 units of plasma in the first 24 hours, the presence of a major brain injury or pelvic fracture and the need for major surgery. In contrast, factors significantly associated with early tPA-R included receiving > 4 units of blood in the first 24 hours and the presence of a major chest injury or long bone fracture. VTE was present in 14.2% of these patients and tPA-R at 12 hours was found to be an independent risk factor for VTE with a hazard ratio of 5.57.

Conclusions: These findings of early dysregulated fibrinolysis have implications for both the timing of initiation and choice of agent used for post-traumatic VTE prophylaxis.

- What opportunities for training and professional development has the project provided?
 - i. All of the clinical research coordinators (CRC) participated in web-based training on the data definitions and the use of the CRF. Selected CRC from the 5 centers participating in CLOTT-2 received hands-on training on how to perform the TEG analyses. In several centers, research residents and trauma fellows have been involved in the analysis of the data in both CLOTT 1 and 2 and in writing papers and abstracts.
- How were the results disseminated to communities of interest?
 - i. The sentinel paper on the results of **CLOTT Part 1** has been published in *JAMA Surgery*. This paper has attracted a high level of interest from trauma and critical care surgeons nation-wide as it has implications for treatment. The results were also presented at the Detroit Trauma Symposium and the Region 7 Annual Trauma Update in 2021. Additional abstracts from the CLOTT Part 1 data base have been submitted to meetings occurring in 2022. The first analysis of **CLOTT Part 2** was accepted and presented at the 2022 Western Trauma Association annual meeting. The corresponding paper has been submitted for publication in the Journal of Trauma and Acute Care Surgery.
- What do you plan to do during the next reporting period to accomplish the goals?
 - i. Not applicable (final report)

4. IMPACT

- What was the impact on the development of the principal discipline(s) of the project?
 - i. Because of the success of CLOTT, the PI and other members of CLOTT were invited to join the NIH Network of Networks and the steering committee for ACTIV (Accelerating COVID-17 Therapeutic Interventions and Vaccines) focusing on the clotting disorders in COVID patients which are very similar to those in trauma patients. All 17 CLOTT centers are invited to participate in the ACTIV anticoagulation trials depending upon their interest and the number of COVID-17 positive patients at their centers. There is a major interest in a follow-on prospective study to investigate safety and efficacy of the algorithm proposed in our CLOTT-1 paper related to observation alone for small asymptomatic pulmonary clots.
- What was the impact on other disciplines?
 - i. Pulmonary clots are frequently seen on CT scans in both surgical and medical patients. When seen on admission scans, they are more likely to be related to inflammatory conditions rather than embolic from DVT. Our observations have major impact on the understanding of primary pulmonary clots and perhaps more importantly on their treatment.
- What was the impact on technology transfer?

- i. Nothing to report
- What was the impact on society beyond science and technology?
 - i. Patients who have developed VTE often require prolonged treatment with anticoagulants. These have major life-changing effects on these patients including potential bleeding complications, costs and life-limiting activities. If there is no need to treat some of these clots, as we have suggested in CLOTT 1, we can make major changes in patient care. Similarly, if tPA-R is an early indicator of the need for early prophylaxis, we have moved the needle on preventing VTE and tPA-R and SD can be utilized as a method of delivering “precision medicine” to those most in need.

5. CHANGES/PROBLEMS

- Changes in approach and reasons for change
 - i. We requested an additional 3-month no cost extension to allow more time to analyze data from CLOTT Part 2.

- Actual or anticipated problems or delays and actions or plans to resolve them

Some sites had to suspend enrollment in CLOTT Part 1 and 2 due to COVID-19 research activities restrictions. These events were reported to HRPO. These suspensions particularly impacted CLOTT Part 2 - which included face-to-face consenting of the patient. Therefore, we applied for and received approval of an additional no-cost extension to continue enrollment at four CLOTT Part 2 sites for as long as financially feasible.

- Changes that had a significant impact on expenditures
 - i. Nothing to report
- Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
 - i. Nothing to report

6. PRODUCTS

Publications, conference papers and presentations

Journal publications:

- Publication in *JAMA Surgery*: M. Margaret Knudson MD, Ernest E. Moore MD, Lucy Z. Kornblith MD, Amy M. Shui MA, Scott Brakenridge MD, Brandon Bruns MD, Mark D. Cipolle MD, Todd W. Costantini MD, Bruce A. Crookes MD, Elliot R. Haut MD, Andy Kerwin MD, Laszlo N. Kiraly MD, Lisa M. Knowlton MD, Matthew J. Martin MD, Michelle K. McNutt MD, David J. Milia MD, Alicia Mohr MD, Ram Nirula MD, Fredrick B/ Rogers MD, Thomas M. Scalea MD, Sherry L. Sixta MD, David A. Spain MD, Charles E. Wade PhD, George C. Velmahos, MD for the CLOTT Study Group. Post-traumatic Pulmonary Thromboembolism: Challenging Traditional Paradigms. Published online December 15, 2021. Doi:10.1001/jamasurg.20216356.

Books or other non-periodical, one-time publications:

- None

Other publications, conference papers and presentations:

Knudson MM, Moore HB, Moore EE, Kornblith LK, Kiraly LN, Bruns B, McNutt M, Wade CE, Sauaia A. Tissue Plasminogen Activator Resistance is an Early Predictor of Post-Traumatic Venous Thromboembolism: A Prospective Study from the CLOTT Research Group. Accepted for Presentation at the Western Trauma Association Annual Meeting, Big Sky Montana February 20-25, 2022. Paper submitted to the Journal of Trauma and Acute Care Surgery.

Lombardo SR, McCrum ML, Knudson MM et al: Weight-based enoxaparin in young trauma patients: an analysis of the CLOTT-1 registry. Accepted for presentation at the Western Trauma Association Annual Meeting, Big Sky Montana February 20-25, 2022. Paper submitted to the Journal of Trauma and Acute Care Surgery.

Website(s) or other Internet site(s):

- None

Technologies or techniques:

- None

Inventions, patent applications, and/or licenses:

- None

Other Products:

- None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals who have worked on the project?

Prime Award at National Trauma Institute d/b/a Coalition for National Trauma Research

Name	Project Role	Nearest person month worked	Contribution to the project
Mary Knudson	Principal Investigator	1	Oversight of entire project (in addition to the effort on the UCSF subaward)
Ernest Moore	Co-Investigator	1	Lead site investigator for Part 2 (in addition to the effort on the Denver Health subaward)
Michelle Price	Project Manager	1	Oversight and management of daily project activities across 17 data collection sites
Lizette Villarreal	Research Coordinator	1	Assists with regulatory oversight and coordination; maintains research materials; assists with DoD report submissions
Amy Flores	Project Support	1	Manage subawards

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Nothing to report

What other organizations were involved as partners?

Site	Institution	PI	Contribution
1	UC San Francisco	Mary Knudson	Lead site; data coordinating center; data analysis; clinical site
2	Christiana Healthcare	Sherry Sixta	Clinical site
3	Medical College of Wisconsin	David Milia	Clinical site
4	Medical University of South Carolina Charleston	Bruce Crookes	Clinical site
5	Johns Hopkins University	Elliott Haut	Clinical site
6	UTHSC Houston	Michelle McNutt	Clinical site
7	University of Florida Health - Jacksonville	Andrew Kerwin	Clinical site
8	University of Florida – Gainesville	Alicia Mohr	Clinical site
9	Oregon Health and Science University	Laszlo Kiraly	Clinical site
10	Denver Health Medical System	Ernest Moore	Clinical site; analyzed samples for
11	University of Utah	Raminder Nirula	Clinical site
12	Lancaster General Hospital	Frederick Rogers	Clinical site
13	Stanford University	David Spain	Clinical site
14	University of Maryland-R. Adams Cowley Shock Trauma	Brandon Bruns	Clinical site
15	UC San Diego-Hillcrest	Todd Costantini	Clinical site
16	Massachusetts General Hospital	George Velmahos	Clinical site
17	Scripps Mercy Hospital	Matthew Martin	Clinical site
18	University of Colorado - Denver	Angela Sauaia	Data analysis

8. SPECIAL REPORTING REQUIREMENTS

- Quad Chart – Included in Appendices

9. APPENDICES

- Quad Chart
- CLOTT Part 1 and 2 HRPO Closeout Status Table
- CLOTT Part 1 Products
- CLOTT Part 2 Products

The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

ERMS/Log Number: BA160400

Award Number: W81XWH-17-1-0673

PI: Mary Knudson

Org: National Trauma Institute

Award Amount: \$4,262,854



Study

1. To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA).
2. To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.

Approach

This is a multi-center, prospective, observational trial performed at 17 level I trauma centers. All injured civilian adult patients in the age range of 18-40 years were screened and those who are found to have PE on a CTA were enrolled. Data were collected and uploaded into REDCap to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. Furthermore, five of these trauma centers enrolled a cohort of patients admitted to their ICU and collect blood samples that were subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown).

The Pathogenesis of Post-Traumatic Pulmonary Emboli

THE CLOTT STUDY GROUP



Activities CY	18	19	20	21
Adapt CLOTT Protocol for DoD Funded Status				
Subcontract with all study sites				
Patient enrollment				
Data Analysis and Knowledge Translation				

Timeline adjusted for 2nd 12mo NCE

Updated: 1/12/2022

Goals/Milestones

CY18 Goal – Adapt Protocol

- ✓ Obtain IRB and HRPO approval for lead site
- ✓ Obtain IRB and HRPO approval for all sites

CY18 Goal – Subcontracts

- ✓ Sub Awards issued for all sites

CY18 - 21 Goal – Patient Enrollment

- ✓ Aim 1 enrollment completed
- ✓ Aim 2 enrollment completed

CY21 Goal – Data Analysis and Knowledge Translation

- ✓ Analyze data (in process)
- ✓ Disseminate findings (in process)

Budget Expenditure to Date

Projected Expenditures: \$4,262,853

Actual Expenditures: \$4,260,450.82

**CLOTT Part 1 and Part 2 HRPO
Close Out Status**

		Protocol	Date Submitted to HRPO	Date Approved by HRPO	Notes
University of California San Francisco	A-20432.1a	Protocol 1	3/24/22	4/4/22	Complete
University of California San Francisco	A-20432.2a	Protocol 2	3/24/22	4/4/22	Complete
Christiana Health Care System	A-20432.1q	Protocol 1	4/8/21	6/8/21	Complete
Denver Health and Hospital Authority	A-20432.1g	Protocol 1	4/6/22	4/1/22	Complete
Denver Health and Hospital Authority	A-20432.2d	Protocol 2			Will submit closure, on hold as they are inputting data
Johns Hopkins University	A-20432.1r	Protocol 1	3/24/22		Submitted closure to HRPO
Lancaster General Hospital	A-20432.1c	Protocol 1	4/8/21	6/8/21	Complete
Massachusetts General Hospital	A-20432.1f	Protocol 1	6/1/21	1/31/22	Complete
Medical College of Wisconsin	A-20432.1l	Protocol 1			IRB closure pending
Medical University of South Carolina	A-20432.1s	Protocol 1	2/12/21	4/12/21	Complete
Oregon Health and Science University	A-20432.1k	Protocol 1	3/24/22		Submitted closure to HRPO
Oregon Health and Science University	A-20432.2e	Protocol 2	3/24/22		Submitted closure to HRPO
Scripps Health	A-20432.1d	Protocol 1	12/7/20	7/28/21	Complete
Stanford University	A-20432.1h	Protocol 1	4/12/21	6/8/21	Complete
University of California San Diego	A-20432.1j	Protocol 1	12/7/20	2/10/21	Complete
University of Florida, Gainesville	A-20432.1o	Protocol 1	6/10/21	10/29/21	Complete
University of Florida, Jacksonville	A-20432.1e	Protocol 1	12/7/20	10/29/21	Complete
University of Maryland Medical Center, Baltimore	A-20432.1p	Protocol 1	12/7/20	2/9/21	Complete
University of Maryland Medical Center, Baltimore	A-20432.2c	Protocol 2	12/7/20	2/9/21	Complete
University of Texas Health Science Center	A-20432.1b	Protocol 1	3/4/22	3/24/22	Complete
University of Texas Health Science Center	A-20432.2b	Protocol 2	3/4/22	3/24/22	Complete
University of Utah	A-20432.1n	Protocol 1	5/13/21	6/8/21	Complete

Challenging Traditional Paradigms in Posttraumatic Pulmonary Thromboembolism

M. Margaret Knudson, MD; Ernest E. Moore, MD; Lucy Z. Kornblith, MD; Amy M. Shui, MA; Scott Brakenridge, MD; Brandon R. Bruns, MD; Mark D. Cipolle, MD; Todd W. Costantini, MD; Bruce A. Crookes, MD; Elliot R. Haut, MD; Andrew J. Kerwin, MD; Laszlo N. Kiraly, MD; Lisa M. Knowlton, MD; Matthew J. Martin, MD; Michelle K. McNutt, MD; David J. Milia, MD; Alicia Mohr, MD; Ram Nirula, MD; Fredrick B. Rogers, MD; Thomas M. Scalea, MD; Sherry L. Sixta, MD; David A. Spain, MD; Charles E. Wade, PhD; George C. Velmahos, MD

 Supplemental content

IMPORTANCE Pulmonary clots are seen frequently on chest computed tomography performed after trauma, but recent studies suggest that pulmonary thrombosis (PT) and pulmonary embolism (PE) after trauma are independent clinical events.

OBJECTIVE To assess whether posttraumatic PT represents a distinct clinical entity associated with the nature of the injury, different from the traditional venous thromboembolic paradigm of deep venous thrombosis (DVT) and PE.

DESIGN, SETTING, AND PARTICIPANTS This prospective, observational, multicenter cohort study was conducted by the Consortium of Leaders in the Study of Traumatic Thromboembolism (CLOTT) study group. The study was conducted at 17 US level I trauma centers during a 2-year period (January 1, 2018, to December 31, 2020). Consecutive patients 18 to 40 years of age admitted for a minimum of 48 hours with at least 1 previously defined trauma-associated venous thromboembolism (VTE) risk factor were followed up until discharge or 30 days.

EXPOSURES Investigational imaging, prophylactic measures used, and treatment of clots.

MAIN OUTCOMES AND MEASURES The main outcomes of interest were the presence, timing, location, and treatment of any pulmonary clots, as well as the associated injury-related risk factors. Secondary outcomes included DVT. We regarded pulmonary clots with DVT as PE and those without DVT as de novo PT.

RESULTS A total of 7880 patients (mean [SD] age, 29.1 [6.4] years; 5859 [74.4%] male) were studied, 277 with DVT (3.5%), 40 with PE (0.5%), and 117 with PT (1.5%). Shock on admission was present in only 460 patients (6.2%) who had no DVT, PT, or PE but was documented in 11 (27.5%) of those with PE and 30 (25.6%) in those with PT. Risk factors independently associated with PT but not DVT or PE included shock on admission (systolic blood pressure <90 mm Hg) (odds ratio, 2.74; 95% CI, 1.72-4.39; $P < .001$) and major chest injury with Abbreviated Injury Score of 3 or higher (odds ratio, 1.72; 95% CI, 1.16-2.56; $P = .007$). Factors associated with the presence of PT on admission included major chest injury (14 patients [50.0%] with or without major chest injury with an Abbreviated Injury Score >3 ; $P = .04$) and major venous injury (23 [82.1%] without major venous injury and 5 [17.9%] with major venous injury; $P = .02$). No deaths were attributed to PT or PE.

CONCLUSIONS AND RELEVANCE To our knowledge, this CLOTT study is the largest prospective investigation in the world that focuses on posttraumatic PT. The study suggests that most pulmonary clots are not embolic but rather result from inflammation, endothelial injury, and the hypercoagulable state caused by the injury itself.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: M. Margaret Knudson, MD, Department of Surgery, University of California, San Francisco, 1001 Potrero Ave, Ward 3A, San Francisco, CA 94110 (peggy.knudson@ucsf.edu).

Venous thromboembolism (VTE) remains a leading cause of morbidity and mortality after trauma.^{1,2} The long-standing assumption that deep vein thrombosis (DVT) and pulmonary emboli (PE) are manifestations of the same pathology has driven prophylactic guidelines with the hypothesis that preventing DVT will lead to a reduction in PE. However, in recent years, many have questioned the association between DVT and pulmonary clots in patients with major injury, concluding instead that pulmonary thrombosis (PT) can arise de novo without DVT and may be a manifestation of local inflammation.²⁻⁷ In fact, pulmonary clots are frequently detected early after injury on computed tomographic scans (CTs) of the chest in both military and civilian patients with trauma and many are asymptomatic, raising the question of whether posttraumatic clots arise in situ and are not embolic in nature.⁸⁻¹⁰ Given the implications that this could have on prophylactic measures (specifically prophylactic vena cava filters) and potentially even on treatment, a large-scale, multicenter investigation characterizing posttraumatic PT was needed.

To address this important issue, a number of experts in the field of posttraumatic VTE came together to form the Consortium of Leaders in the Study of Traumatic Thromboembolism (CLOTT).¹¹ The 17 CLOTT trauma surgeons, each of whom represents a level I American College of Surgeons-verified trauma center, agreed to work collaboratively in this prospective study with the main objective of defining the pathogenesis of and risk factors for posttraumatic PT. We hypothesized that posttraumatic PT represents a distinct clinical entity with identifiable risk factors primarily associated with the nature and the severity of the injury, different from the traditional venous thromboembolic paradigm of DVT and PE.

Methods

Study Design and Data Collection

This prospective, multicenter, observational cohort study (CLOTT 1) was conducted at 17 major trauma centers in the US. Permission to conduct the study was obtained at all 17 institutional review boards and included a waiver of informed consent given the observational nature and minimal risk to the patients related to this research. The study was also approved by the US Department of Defense Human Research Protection Office. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The treating surgeon was at liberty to order any imaging studies related to VTE and to choose the methods used for prophylaxis and the treatment of any clots detected on imaging. The comprehensive electronic case report form was designed exclusively for this study. Patient data were entered into the secure central Research Electronic Data Capture (REDCap) system located at the University of California, San Francisco. Each patient was given a unique record identification number in the database to ensure patient confidentiality. Each site has access to its own data; however, because potentially identify-

Key Points

Question Are all pulmonary clots seen on chest imaging after trauma pulmonary emboli (PE), or are some de novo pulmonary thrombosis (PT) with distinct risk factors?

Findings In this cohort study of 7880 injured patients, 277 had deep venous thrombosis, 40 had PE, and 117 had PT. Factors significantly associated with the development of PT but not deep venous thrombosis or PE include the presence of shock on admission and major chest injury.

Meaning This cohort study provides further evidence that not all pulmonary clots are PE and sets the stage for future studies into the pathophysiology and treatment of de novo PT.

ing data (age, sex, and date of admission) were included, only the main study principal investigator (Dr Knudson) had access to the entire data set as well as the codes for each participating trauma center. Before the start of the study, webinars were conducted to train clinical research coordinators at each site on the use of the case report form and entry into REDCap. A data dictionary and a standard operating manual were also developed and distributed. Periodic quality checks of the data entered into REDCap were performed at the main principal investigator site and included identification of missing data points as well as data errors.

Patients were screened for inclusion in this study if they were admitted to any of the participating trauma centers during the study period (January 1, 2018, to December 31, 2020). Because this study was funded by the US Department of Defense, the age criteria were matched to military personnel in the deployed setting (18-40 years of age). Patients who remained in the hospital for at least 48 hours and who had at least 1 previously identified posttraumatic VTE risk factor were considered eligible for the study¹² (Table 1). Data collected prospectively from the electronic medical record and other hospital sources included patient demographic characteristics, admission vital signs and laboratory data, mechanism of injury, blood products and procoagulants administered during the first 24 hours, preexisting and postinjury VTE risk factors, Abbreviated Injury Scale (AIS) and Injury Severity Scale scores, length of stay, days in the intensive care unit, days receiving ventilatory support, discharge disposition, and cause of any deaths. Extensive data were collected on VTE prophylaxis used, including when it was initiated, chemical prophylactic drugs ordered, missed doses (including the reason for holding doses), and any complications associated with prophylaxis. Data were also collected on the use of vena cava filters as prophylactic devices. The primary outcome of interest was the presence of any pulmonary clot seen on computed tomography. We collected dates of all scans performed and the indications for the scan (ie, initial posttrauma evaluation, suspected PE, retained hemothorax, pneumonia or pneumothorax evaluation). Of particular interest was the location of pulmonary clots (side of the chest, main pulmonary artery, lobar artery, segmental artery, or subsegmental pulmonary artery). The treatment of pulmonary clots and any complications associated with treatment were also entered into the database.

Table 1. Patient Characteristics and Potential Risk Factors of Venous Thromboembolism^a

Variable	Overall (N = 7880)	DVT only (n = 277)	PE (n = 40)	PT (n = 117)	None (n = 7446)
Age at admission, mean (SD), y	29.1 (6.4)	29.8 (6.2)	27.7 (5.3)	29.9 (6.4)	29.1 (6.4)
Sex					
Male	5859 (74.4)	218 (78.7)	28 (70.0)	91 (77.8)	5522 (74.2)
Female	2021 (25.7)	59 (21.3)	12 (30.0)	26 (22.4)	1924 (25.8)
Head injury	2341 (29.7)	137 (49.5)	10 (25.0)	35 (29.9)	2159 (29.0)
Spinal cord injury	343 (4.4)	30 (10.8)	3 (7.5)	11 (9.4)	299 (4.0)
Shock on admission (SBP <90 mm Hg)	543 (6.9)	42 (15.2)	11 (27.5)	30 (25.6)	460 (6.2)
Chest injury	2487 (31.6)	123 (44.4)	22 (55.0)	62 (53.0)	2280 (30.6)
Abdominal injury	1716 (21.8)	95 (34.3)	17 (42.5)	46 (39.3)	1558 (20.9)
Pelvic fracture	1408 (17.9)	68 (24.5)	15 (37.5)	31 (26.5)	1294 (17.4)
Long bone fracture	2521 (32.0)	87 (31.4)	16 (40.0)	46 (39.3)	2372 (31.9)
Venous injury	462 (5.9)	36 (13.0)	9 (22.5)	15 (12.8)	402 (5.4)
Femoral venous catheter	521 (6.6)	71 (25.6)	12 (30.0)	26 (22.2)	412 (5.5)
Major operative procedure (≥1 h)	5815 (73.8)	229 (82.7)	38 (95.0)	103 (88.0)	5445 (73.1)
≥4 d of ventilatory support	1190 (15.1)	137 (49.5)	26 (65.0)	45 (38.5)	982 (13.2)
Tranexamic acid administration	648 (8.2)	48 (17.3)	10 (25.0)	11 (9.4)	579 (7.8)
Coagulopathy (INR>1.5)	224 (2.8)	25 (9.0)	5 (12.5)	9 (7.7)	185 (2.5)
History of VTE	31 (0.4)	0 (0.0)	0 (0.0)	2 (1.7)	29 (0.4)
Current cancer	26 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	24 (0.3)
Pregnancy or recently post partum (within last 3 mo)	85 (1.1)	1 (0.4)	0 (0.0)	1 (0.9)	83 (1.1)
Hormone therapy	163 (2.1)	6 (2.2)	2 (5.0)	3 (2.6)	152 (2.0)
Inflammatory bowel disease	25 (0.3)	1 (0.4)	0 (0.0)	1 (0.9)	23 (0.3)
Heparin					
5000 U 2 times daily	137 (1.7)	10 (3.6)	3 (7.5)	5 (4.3)	119 (1.6)
5000 U 3 times daily	1142 (14.5)	69 (24.9)	10 (25.0)	20 (17.1)	1043 (14.0)
Enoxaparin					
30 mg Twice daily	3541 (44.9)	76 (27.4)	10 (25.0)	46 (39.3)	3409 (45.8)
40 mg Once daily	1235 (15.7)	54 (19.5)	3 (7.5)	9 (7.7)	1169 (15.7)
Prophylaxis					
Other	93 (1.2)	3 (1.1)	0 (0.0)	1 (0.9)	89 (1.2)
No	750 (9.5)	22 (7.9)	6 (15.0)	15 (12.8)	707 (9.5)

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary emboli; PT, pulmonary thrombosis; SBP, systolic blood pressure; VTE, venous thromboembolism.

^a Data are presented as number (percentage) of patients unless otherwise indicated. No prophylaxis indicates not receiving prophylaxis when DVT, PT, or PE was detected.

For the secondary outcome of interest, DVT, detailed data points included the date of any duplex ultrasound examinations performed (or CT where DVT was noted), symptoms precipitating the examination (if not part of a surveillance program), the location of any clots detected, and their treatment (including complications associated with treatment). Because some of the centers conducted routine duplex examinations as part of a surveillance program, the number of studies at each of the 17 centers varied.¹³ Enrolled patients were followed up until discharge or for up to 30 days from admission.

The number of patients to be included in the study was based on an estimated 4% overall incidence of pulmonary clots. The number of years to complete the study was estimated at 2 given the admission rate of injured patients to these trauma centers in the allowable age range of 18 to 40 years.

Definitions

On the basis of previous work,^{1-4,11,12} the CLOTT group developed the following set of definitions for each of the variables of interest: shock: systolic blood pressure less than 90 mm Hg; major head injury: AIS score of 3 or higher; major chest injury: AIS score of 3 or higher; major abdominal injury: AIS score of 3 or higher; long bone fracture: lower-extremity fracture above the ankle; venous injury: a major named vein that required operative repair or ligation; major operation: post-trauma procedure that lasted at least 1 hour and required general anesthesia; and coagulopathy: international normalized ratio greater than 1.5 on admission. Of importance, for the purposes of this study, pulmonary clots seen in association with any DVT that developed within the 30 days were considered PE, whereas isolated clots without known DVT were considered de novo PT.

Table 2. Results of the Unadjusted Multinomial Logistic Regression Models^a

Variable	DVT only vs none (n = 277)		PE vs none (n = 40)		PT vs none (n = 117)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age at admission	1.02 (1.00-1.04)	.06	0.97 (0.92-1.02)	.19	1.02 (0.99-1.05)	.16
Sex (female vs male)	0.78 (0.58-1.04)	.09	1.23 (0.62-2.42)	.55	0.83 (0.53-1.29)	.40
Head injury	2.40 (1.88-3.05)	<.001	0.82 (0.40-1.67)	.58	1.05 (0.70-1.56)	.83
Spinal cord injury	2.90 (1.95-4.31)	<.001	1.94 (0.59-6.32)	.27	2.48 (1.32-4.66)	.005
Shock on admission (SBP <90 mm Hg)	2.71 (1.93-3.82)	<.001	5.76 (2.86-11.6)	<.001	5.24 (3.42-8.01)	<.001
Chest injury	1.81 (1.42-2.31)	<.001	2.77 (1.48-5.17)	.001	2.55 (1.77-3.68)	<.001
Abdominal injury	1.97 (1.53-2.54)	<.001	2.79 (1.49-5.24)	.001	2.45 (1.68-3.56)	<.001
Pelvic fracture	1.55 (1.17-2.05)	.002	2.85 (1.50-5.43)	.001	1.71 (1.13-2.60)	.01
Long bone fracture	0.98 (0.76-1.27)	.88	1.43 (0.76-2.69)	.27	1.39 (0.95-2.02)	.09
Venous injury	2.62 (1.82-3.77)	<.001	5.09 (2.41-10.8)	<.001	2.58 (1.48-4.47)	<.001
Femoral venous catheter	5.88 (4.41-7.84)	<.001	7.32 (3.69-14.5)	<.001	4.88 (3.12-7.63)	<.001
Major operative procedure (≥1 h)	1.75 (1.28-2.40)	<.001	6.98 (1.68-28.9)	.007	2.70 (1.54-4.74)	<.001
≥4 d of ventilatory support	6.44 (5.04-8.23)	<.001	12.2 (6.36-23.5)	<.001	4.11 (2.82-6.01)	<.001
Tranexamic administration	2.49 (1.80-3.43)	<.001	3.96 (1.92-8.13)	<.001	1.23 (0.66-2.30)	.52
Coagulopathy (INR >1.5)	3.89 (2.52-6.02)	<.001	5.61 (2.17-14.5)	<.001	3.27 (1.63-6.56)	<.001
History of VTE	0	.15	0	.58	4.45 (1.05-18.9)	.04
Current cancer	2.25 (0.53-9.56)	.27	0	.61	0	.39
Pregnancy or recently post partum (within last 3 mo)	0.32 (0.04-2.32)	.26	0	.34	0.76 (0.11-5.54)	.79
Hormone therapy	1.06 (0.47-2.42)	.89	2.53 (0.60-10.6)	.20	1.26 (0.40-4.02)	.69
Inflammatory bowel disease	1.17 (0.16-8.69)	.88	0	.62	2.78 (0.37-20.8)	.32
Heparin						
5000 U 2 times daily	2.31 (1.20-4.45)	.01	4.99 (1.52-16.4)	.008	2.75 (1.10-6.86)	.03
5000 U 3 times daily	2.04 (1.54-2.69)	<.001	2.05 (1.00-4.20)	.05	1.27 (0.78-2.06)	.34
Enoxaparin						
30 mg Twice daily	0.45 (0.34-0.58)	<.001	0.39 (0.19-0.81)	.01	0.77 (0.53-1.11)	.16
40 mg Once daily	1.30 (0.96-1.76)	.09	0.44 (0.13-1.41)	.17	0.45 (0.23-0.89)	.02
Prophylaxis						
Other	0.91 (0.28-2.88)	.87	0	.33	0.71 (0.10-5.16)	.74
No	0.82 (0.53-1.28)	.39	1.68 (0.70-4.02)	.24	1.40 (0.81-2.42)	.23

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; OR, odds ratio; PE, pulmonary emboli; PT, pulmonary thrombosis; SBP, systolic blood pressure; VTE, venous thromboembolism.

^a For associations with $P < .10$, these variables entered the backward elimination

selection process for multivariable logistic regression model development. Likelihood ratio test P value is reported if there were 0 events in a variable category.

Data Analysis

For the purposes of this investigation, the patients were assigned to 1 of 4 categories: no VTE, DVT only, PE, and PT only. Risk factor stratification was based on previous work¹² that included 1602 episodes captured retrospectively from the American College of Surgeons National Trauma Data Bank in 2004. In that study (which did not separate pulmonary clots from DVT but rather focused on the conglomerate of VTE, which included DVT and PE and/or PT), Knudson et al¹² identified 6 high-risk factors for the development of VTE (odds ratio [OR] of 2-3): age of 40 years or older, a pelvic fracture, lower-extremity fracture (above the ankle), shock on admission, spinal cord injury, and major head injury. Characteristics associated with a very high risk of VTE (OR for VTE of 4-10) were a major operative procedure, the presence of a major venous injury, the need for mechanical ventilatory sup-

port for more than 3 days, and the presence of 2 or more of the high-risk factors.

Statistical Analysis

Tabulations or summary statistics of potential risk factors for VTE were described by each outcome category (DVT only, PE, PT only, or none). Each candidate risk factor was included in unadjusted multinomial logistic regression models, with the none category as the reference group for the outcome. Candidate variables that had associations with $P < .10$ from the unadjusted analyses were included in multivariable binary logistic regression models for each outcome category, using the reference group none, and covariates not attaining significance at the $P < .05$ level were sequentially eliminated until all covariates were significantly associated with each outcome category.

High-risk and very high-risk factors were defined as listed above.

All primary analysis variables had complete data for the 7880 study participants. Multicollinearity issues were addressed if any variable had a correlation coefficient of 0.6 or higher or a variance inflation factor of 2 or higher. Hypothesis tests were 2-sided and the significance threshold was set to $P < .05$. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc). A secondary analysis to identify factors associated with the presence of PT on the admitting CT was performed using Fisher exact tests.

Results

During the 2-year period, 7880 patients (mean [SD] age, 29.1 [6.4] years; 5859 [74.4%] male) were enrolled in this study (Table 1). Data on race and ethnicity as well as insurance status were collected because such data are generally required on any federal grant to ensure lack of bias in enrollment. However, because these categories do not have any known association with VTE, we did not analyze these data. A total of 277 patients (3.5%) were diagnosed with DVT only during their hospitalization for trauma, 40 (0.5%) with both DVT and pulmonary clot (presumed PE), and 117 (1.5%) with pulmonary clot only (presumed PT). Shock on admission was present in only 460 patients (6.2%) who had no DVT, PT, or PE but was documented in 11 (27.5%) of those with PE and 30 (25.6%) in those with PT (Table 1). Compared with those with no pulmonary or deep venous clots ($n = 7446$), those with DVT ($n = 277$), PE ($n = 40$), or PT ($n = 117$) were more significantly injured, with higher rates of major chest injury (123 [44.4%] in the DVT group, 22 [55.0%] in the PE group, and 62 [53.0%] in the PT group vs 2280 [30.6%] in those with no pulmonary or deep venous clots), abdominal injury (95 [34.3%] in the DVT group, 17 [42.5%] in the PE group, and 46 [39.3%] in the PT group vs 1558 [20.9%] in those with no pulmonary or deep venous clots), pelvic fracture (68 [24.5%] in the DVT group, 15 [37.5%] in the PE group, and 31 [26.5%] in the PT group vs 1294 [17.4%] in those with no pulmonary or deep venous clots), long bone fracture (87 [31.4%] in the DVT group, 16 [40.0%] in the PE group, and 46 [39.3%] in the PT group vs 2372 [31.9%] in those with no pulmonary or deep venous clots), and venous injury (36 [13.0%] in the DVT group, 9 [22.5%] in the PE group, and 15 [12.8%] in the PT group vs 402 [5.4%] in those with no pulmonary or deep venous clots). Those who developed venous or pulmonary clots after injury were also more likely to require ventilatory support for 4 days or longer (1190 [15.1%] vs 982 [13.2%]). Tranexamic acid was administered to 648 patients and 48 developed DVT, 10 PE, and 11 PT.

Preexisting risk factors for VTE (prior history of VTE, current cancer, pregnancy, hormone therapy, or inflammatory bowel disease) were rare among these relatively young patients. Various chemical VTE prophylactic measures were used during the study, but 8 of the 40 patients with PE (20.0%) and 28 of the 117 patients with PT (23.9%) had clots visible on the admitting CTs before prophylaxis could be initiated (Table 1; eTables 1 and 2 in the [Supplement](#)).

A number of variables appeared to be significantly associated with the diagnoses of DVT alone, PE, and PT in the unadjusted regression model (Table 2). For each year increase in patient age older than 18 years, the odds of DVT vs none increased by 1.8% ($P = .06$), and the odds of PT only vs none increased by 2.1% ($P = .16$). Of interest, all 9 high-risk and very high-risk factors that had previously been identified were still significant in this prospective study as well.¹²

Table 3 contains the results of the multivariable logistic regression analysis. In addition to advancing age (OR, 1.02; 95% CI, 1.00-1.04), injury variables associated with an increased risk of DVT included the presence of major injury to the head (OR, 1.41; 95% CI, 1.05-1.89), spinal cord injury (OR, 1.74; 95% CI, 1.14-2.67), abdominal injury (OR, 1.60; 95% CI, 1.20-2.12), pelvic fracture (OR, 1.36; 95% CI, 1.01-1.84), and a major venous injury (OR, 1.64; 95% CI, 1.09-2.48). Placement of a femoral vein catheter for resuscitation (OR, 2.25; 95% CI, 1.61-3.14), the need for major surgery (OR, 1.56; 95% CI, 1.12-2.21), the need for prolonged ventilatory support (OR, 3.68; 95% CI, 2.72-4.98), and administration of tranexamic acid (OR, 1.65; 95% CI, 1.16-2.35) were all significantly associated with the development of DVT. Risk factors independently associated with the development of PT but not DVT or PE include shock on admission (OR, 2.74; 95% CI, 1.72-4.39), major chest injury (OR, 1.72; 95% CI, 1.16-2.56), and a history of VTE (OR, 5.39; 95% CI, 1.19-24.4). Of the 40 patients with PE, 25 patients (62.5%) developed PE during the first week after injury and 23 (57.0%) had their DVT detected during that first week as well (eTable 2 in the [Supplement](#)).

On further examination of patients with PT only ($n = 117$), 61 (52.1%) had clots on the same side as a chest injury. Of these patients, 28 (23.9%) had clot evident on the admitting chest CT, and an additional 55 scans (47.0%) were positive for PT between days 1 and 7. Of the 89 patients who developed delayed PT, 84 (94.3%) had a prior CT or comparison. Eighty-eight patients (75.2%) with PT in this study were treated with full dose anticoagulation, 14 patients (11.9%) received an inferior vena cava filter, and 15 patients (12.8%) with PT were simply observed. Eight clots were in the main pulmonary artery, 26 were lobar, 28 were segmental, 21 were subsegmental, and 34 were multiple (eTable 1 in the [Supplement](#)). Factors associated with the presence of PT on admission included major chest injury (14 patients [50.0%] with or without major chest injury with an Abbreviated Injury Score >3 ; $P = .04$) and major venous injury (23 [82.1%] without major venous injury and 5 [17.9%] with major venous injury; $P = .02$) (Table 4).

Discussion

The most important finding in this cohort study is that major chest trauma and shock significantly increase the risk of developing PT but not DVT or PE, confirming our hypothesis that PT represents a distinct clinical entity. Chest trauma likely results in inflammation manifested by pulmonary clots that appear to develop early after injury. Severely injured patients who present in shock rapidly develop a hypercoagulable state, which likely contributes to the risk of PT.¹⁴⁻¹⁸ Previous studies¹⁹⁻²¹ sug-

Table 3. Results of the Multivariable Binary Logistic Regression Models

Variable	DVT only vs none (n = 277)		PE vs none (n = 40)		PT vs none (n = 117)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age at admission	1.02 (1.00-1.04)	.048	NA	NA	NA	NA
Head injury	1.41 (1.05-1.89)	.02	NA	NA	NA	NA
Spinal cord injury	1.74 (1.14-2.67)	.01	NA	NA	NA	NA
Shock on admission (SBP <90 mm Hg)	NA	NA	NA	NA	2.74 (1.72-4.39)	<.001
Chest injury	NA	NA	NA	NA	1.72 (1.16-2.56)	.007
Abdominal injury	1.60 (1.20-2.12)	.001	NA	NA	1.58 (1.06-2.36)	.03
Pelvic fracture	1.36 (1.01-1.84)	.046	2.52 (1.31-4.86)	.006	NA	NA
Long bone fracture			NA	NA	NA	NA
Venous injury	1.64 (1.09-2.48)	.02	3.49 (1.60-7.62)	.002	NA	NA
Femoral venous catheter	2.25 (1.61-3.14)	<.001	NA	NA	2.19 (1.32-3.62)	.002
Major operative procedure (≥1 h)	1.56 (1.12-2.21)	.009	NA	NA	2.09 (1.18-3.71)	.01
≥4 d of ventilatory support	3.68 (2.72-4.98)	<.001	10.1 (5.20-19.7)	<.001	2.21 (1.44-3.39)	<.001
Tranexamic acid administration	1.65 (1.16-2.35)	.005	2.48 (1.17-5.26)	.02	NA	NA
Coagulopathy (INR >1.5)	NA	NA	NA	NA	NA	NA
History of VTE	NA	NA	NA	NA	5.39 (1.19-24.4)	.03
Heparin						
5000 U 2 times daily	NA	NA	NA	NA	3.26 (1.27-8.35)	.01
5000 U 3 times per day	NA	NA	NA	NA	NA	NA
Enoxaparin						
30 mg Twice daily	0.52 (0.39-0.70)	<.001	NA	NA	NA	NA
40 mg Once daily	1.55 (1.10-2.18)	.01	NA	NA	NA	NA

Abbreviations: DVT, deep vein thrombosis; INR, international normalized ratio; NA, not applicable; OR, odds ratio; PE, pulmonary emboli; PT, pulmonary thrombosis; SBP, systolic blood pressure; VTE, venous thromboembolism.

gest that fibrinolytic shutdown occurs frequently after severe injury, preventing clot lysis and contributing to the hypercoagulable state. The association between fibrinolytic shutdown and posttraumatic DVT, PE, and PT is the subject of an ongoing study by CLOTT investigators.

The association between trauma and pulmonary clots was established almost a century ago based primarily on autopsy studies of patients with fractures.²² The past 20 years of military operations in Afghanistan and Iraq has precipitated a renewed interest in VTE because rates of pulmonary clots among those who have been injured in combat are reported as high as 9%.^{8,23,24} In both civilian and military medical communities, the traditionally held dogma that DVT leads to pulmonary embolism has been recently challenged.²⁻¹⁰ Perhaps the most compelling evidence to support the development of de novo pulmonary clots was published by Velmahos et al,⁴ who performed computed tomographic venography and computed tomographic pulmonary angiography simultaneously in 247 patients with trauma, finding that 19% had pulmonary clots but only 7% had DVT.

Five of the independent risk factors for DVT identified in this large prospective study (age, major head injury, pelvic fractures, major venous injury, and femoral vein catheters) have been previously reported and are not discussed further in this article.^{1,2,12,14,25-27} The association between PT on admission and the presence of a major venous injury deserves further study. It is potentially possible that these patients had a clot

that embolized before the admitting chest CT. A more likely hypothesis is that the venous injury caused shock and an early hypercoagulable state precipitating the PT. The use of the antifibrinolytic agent tranexamic acid after major trauma has increased since the publication of the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2)²⁸ and MATTERS (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation)²⁹⁻³³ studies, but its association with VTE is hotly debated. In the current study, tranexamic acid administration was associated with increases in the risk of development of DVT by 1.65 times and of PE by 2.48 times (Table 3), but the true risk will require elucidation of the timing and dosing of tranexamic acid. Although the best prophylactic regimen to prevent VTE after trauma continues to be debated, our preliminary results suggest that the 2 doses of enoxaparin used in this study may not offer equivalent protection against DVT, whereas all 4 prophylactic regimens appeared to be effective in preventing PE (Table 3).³⁴⁻⁴² However, the agent and dose analyzed for the analysis were the combination that the patient was receiving at the time DVT, PE, or PT was diagnosed. We did not account for the timing of initiation of prophylaxis or missed doses. In addition, it might well be that different prophylactic regimens are more effective for certain types of injuries but not for others.

Finally, based on our evolving understanding of the pathogenesis of PT, we recommend consideration of observation of posttraumatic, subsegmental PT that are discovered incidentally.

Table 4. Presence or Absence of Pulmonary Thrombosis on Admission in Patients Who Also Had VTE Risk Factors

Variable	Overall (N = 7880)	Outcome		P value
		No PT at admission (n = 7852)	PT at admission (n = 28)	
Shock (SBP <90 mm Hg)				
Absent	7338 (93.1)	7314 (93.1)	24 (85.7)	.12
Present	543 (6.9)	539 (6.9)	4 (14.3)	
Coagulopathy (INR >1.5)				
Absent	7656 (97.1)	7629 (97.1)	27 (96.4)	.56
Present	225 (2.9)	224 (2.9)	1 (3.6)	
Chest injury (AIS score >3)				
Absent	5393 (68.4)	5379 (68.5)	14 (50.0)	.04
Present	2488 (31.6)	2474 (31.5)	14 (50.0)	
Head injury (AIS score >3)				
Absent	5540 (70.3)	5523 (70.3)	17 (60.7)	.30
Present	2341 (29.7)	2330 (29.7)	11 (39.3)	
Abdominal injury (AIS score >3)				
Absent	6165 (78.2)	6146 (78.3)	19 (67.9)	.18
Present	1716 (21.8)	1707 (21.7)	9 (32.1)	
Spinal cord injury				
Absent	7538 (95.6)	7512 (95.7)	26 (92.9)	.35
Present	343 (4.4)	341 (4.3)	2 (7.1)	
Pelvic fracture				
Absent	6273 (82.1)	6453 (82.2)	20 (71.4)	.14
Present	1408 (17.9)	1400 (17.8)	8 (28.6)	
Long bone fracture				
Absent	5360 (68)	5344 (68.1)	16 (57.1)	.23
Present	2521 (32.0)	2509 (31.9)	12 (42.9)	
Venous injury				
Absent	7419 (94.1)	7396 (94.2)	23 (82.1)	.02
Present	462 (5.9)	457 (5.8)	5 (17.9)	
Major operative procedure (≥1 h)				
Absent	2065 (26.2)	2061 (26.2)	4 (14.3)	.20
Present	5816 (73.8)	5792 (73.8)	24 (85.7)	
>4 d of ventilatory support				
Absent	6690 (84.9)	6674 (85)	16 (57.1)	<.001
Present	1190 (15.1)	1190 (15.0)	12 (42.9)	

Abbreviations: AIS, abbreviated injury score; INR, international normalized ratio; PT, pulmonary thrombosis; SBP, systolic blood pressure.

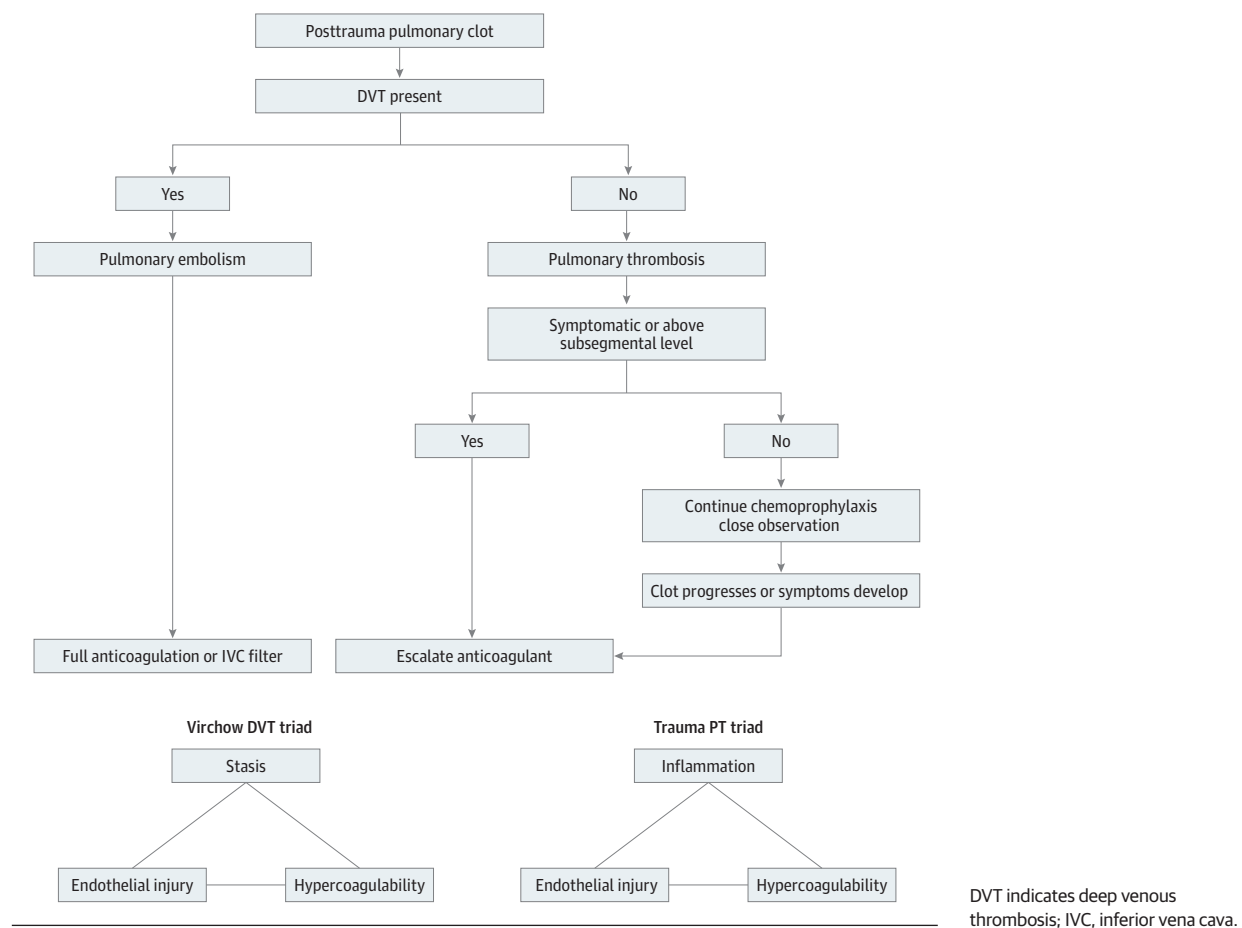
tally and not associated with proximal DVT, a position supported in the recent American College of Chest Physicians guidelines.⁴³ This recommendation may be particularly relevant to patients whose clots are detected on admission or early in their hospital course or in those who are at risk for hemorrhagic complications with anticoagulation. However, the safety of this approach deserves further study. The **Figure** outlines a treatment approach to consider for posttraumatic PT and PE.

Limitations

This study has limitations, including the relatively young age of the patients included, which will affect its applicability in older patients with trauma. In addition, because this was an observational study, the use of prophylactic measures, DVT screening procedures, and the treatment of any clots discov-

ered varied considerably across the 17 centers. Most importantly, we assumed that pulmonary clots not associated with DVT are not embolic, but only 64.2% of patients with DVT and pulmonary clot had a duplex DVT scan close to their CT with positive findings in this study. It is possible that DVT that developed before the PE was simply missed. In addition, most venous duplex examinations are limited in the area of the pelvis and will not detect clots in major abdominal veins, which may also be the source of emboli. On the other hand, the presence of both DVT and pulmonary clot in the same patient during hospitalization does not prove that the pulmonary clot is embolic. The presence of PT on the admitting CT in one-quarter of the patients with PT in our study lends support to the premise that many pulmonary clots are de novo PT and not PE. Despite these limitations, this is, to our knowledge, the largest prospective study to date focused on posttraumatic PT.

Figure. Algorithm for the Treatment of Posttraumatic Pulmonary Thromboembolism (PT) and Proposed New Triad for Posttraumatic PT



Conclusions

This cohort study found that not all pulmonary clots seen on computed tomography of the chest after injury are embolic but instead represent a combination of PE and PT. On the basis of

this study's findings, PT has independent risk factors different than those traditionally associated with VTE. With a focus on the original Virchow DVT triad, this study offers a new PT triad that can guide future research into the role of injury, inflammation, and a hypercoagulable state as factors associated with the development of posttraumatic PT.

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Author Affiliations: Department of Surgery, University of California, San Francisco (Knudson, Kornblith); Department of Surgery, University of Colorado, Denver (Moore); Department of Epidemiology and Biostatistics, University of California, San Francisco (Shui); Department of Surgery, University of Florida, Gainesville (Brakenridge); Now with Department of Surgery, University of Washington, Seattle (Brakenridge, Kerwin, Mohr); Department of Surgery, University of Maryland, Baltimore (Bruns, Scalea); Now with the Department of Surgery, University of Texas Southwestern, Dallas (Bruns); Department of Surgery, Christiana Health Care, Newark, Delaware (Cipolle, Sixta); Now with the Department of

Surgery Lehigh Valley Health, Allentown, Pennsylvania (Cipolle); Department of Surgery, University of California, San Diego (Costantini); Department of Surgery, Medical University of South Carolina, Charleston (Crookes); Department of Surgery, Johns Hopkins University, Baltimore, Maryland (Haut); Now with the Department of Surgery, University of Tennessee, Memphis (Kerwin); Department of Surgery, University of Oregon Health Sciences University, Portland (Kiraly); Department of Surgery, Stanford University, Palo Alto, California (Knowlton, Spain); Department of Surgery, Scripps Mercy Hospital, San Diego, California (Martin); Department of Surgery, University of Texas, Houston (McNutt, Wade); Department of Surgery, Medical College of Wisconsin, Milwaukee (Milia); Department of Surgery, University of Utah, Salt Lake City (Nirula); Department of Surgery, Lancaster General Hospital, Lancaster, Pennsylvania (Rogers); Department of

Surgery, Harvard University, Boston, Massachusetts (Velmahos).

Author Contributions: Dr Knudson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Knudson, Moore, Brakenridge, Cipolle, Costantini, Crookes, Haut, Kerwin, Knowlton, Nirula, Scalea, Spain, Wade, Velmahos.

Acquisition, analysis, or interpretation of data: Knudson, Kornblith, Shui, Brakenridge, Bruns, Cipolle, Costantini, Crookes, Haut, Kerwin, Kiraly, Knowlton, Martin, McNutt, Milia, Mohr, Nirula, Rogers, Sixta, Spain, Wade.

Drafting of the manuscript: Knudson, Moore, Kornblith, Spain.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Knudson, Shui.

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Administrative, technical, or material support:

Knudson, Kornblith, Brakenridge, Bruns, Crookes, Kerwin, Kiraly, Martin, McNutt, Millia, Mohr, Nirula, Sixta, Spain, Wade.

Supervision: Knudson, Moore, Brakenridge, Cipolle, Kerwin, Kiraly, Knowlton, Spain, Wade.

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Journal of Trauma and Acute Care Surgery

Weight-based enoxaparin thromboprophylaxis in young trauma patients: analysis of the CLOTT-1 registry --Manuscript Draft--

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Corresponding Author:	Sarah R Lombardo, MD, MSc University of Utah Medical Center: University of Utah Hospital SALT LAKE CITY, UT UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Utah Medical Center: University of Utah Hospital
Corresponding Author's Secondary Institution:	
First Author:	Sarah R Lombardo, MD, MSc
First Author Secondary Information:	
Order of Authors:	Sarah R Lombardo, MD, MSc
	Marta L Mccrum, MD MPH
	M Margaret Knudson, MD
	Ernest E Moore, MD
	Lucy Z Kornblith, MD
	Amy M Shui, MA
	Scott Brakenridge, MD
	Brandon R Bruns, MD
	Mark D Cipolle, MD
	Todd W Costantini, MD
	Bruce A Crookes, MD
	Elliot R Haut, MD
	Andrew J Kerwin, MD
	Laszlo N Kiraly, MD
	Lisa M Knowlton, MD
	Matthew J Martin, MD
	Michelle K McNutt, MD
	David J Milia, MD
	Alicia Mohr, MD
	Frederick B Rogers, MD
	Thomas M Scalea, MD

	Sherry L Sixta, MD
	David A Spain, MD
	Charles E Wade, PhD
	George C Velmahos, MD
	Ram Nirula, MD
	Jade Nunez, MD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED STATES
Abstract:	Introduction : Optimal venous thromboembolism (VTE) enoxaparin prophylaxis dosing remains elusive. Weight-based (WB) dosing safely increases anti-factor-Xa levels without the need for routine monitoring but it is unclear if it leads to lower VTE risk. We hypothesized that early (< 2 days) initiation of WB dosing would decrease VTE risk compared to standard fixed dosing (SFD). Methods: Patients from the prospective, observational CLOTT-1 registry receiving prophylactic enoxaparin (n=5539) were categorized as WB (0.45-0.55 mg/kg BID) or SFD (30mg BID, 40mg qDay). Multivariate logistic regression was used to generate a predicted probability of VTE for WB and SFD patients. Results : Of 4460 patients analyzed, 1082 (24.3%) were WB and 3378 (75.7%) were SFD. Mean age and Injury Severity Score were similar between groups but obesity was higher in the SFD cohort. Unadjusted VTE rates were comparable (WB 3.1% vs. SFD 4.0%; p=0.167). Early prophylaxis was associated with lower VTE rate (3.0% vs. 8.1%; p < 0.001) and DVT (2.1% vs. 7.2%; p < 0.001), but not PE (p = 0.175). After adjustment, VTE incidence did not differ by dosing strategy (aOR 0.84, 95% CI 0.51 – 1.37), however early administration was associated with a significant reduction in VTE (aOR 0.61, 95% CI 0.42 – 0.89). Conclusion : WB prophylaxis in young trauma patients is not associated with reduced VTE rate when compared to SFD. The timing of the initiation of chemoprophylaxis may be more important than the dosing strategy. Further studies need to reconcile this disconnect across a wider age and comorbidity spectrum. Level of Evidence: Level IV, therapeutic/care management
Opposed Reviewers:	

To Whom It May Concern:

I am writing to request your consideration of our original research manuscript, “Weight-based enoxaparin thromboprophylaxis in young trauma patients: analysis of the CLOTT-1 registry” for publication in the Journal of Trauma. This observational cohort study is a secondary analysis of the multicenter Comparative Effectiveness Analysis of Venous Thromboembolism in Trauma Patients (CLOTT-1) registry. The abstract has been accepted for presentation at the 51st Western Trauma Association Annual Meeting.

The need for chemoprophylaxis against venous thromboembolism (VTE) after trauma is well-recognized, however debate remains regarding optimal dosing strategies. Our study sought to evaluate the efficacy of weight-based enoxaparin against standard fixed-dose enoxaparin for prophylaxis against deep vein thrombosis (DVT) and pulmonary embolism (PE). We used forward stepwise multivariate logistic regression analysis with to adjust for potential confounders, including timing of VTE prophylaxis initiation and missed doses. Ultimately, we did not find weight-based prophylaxis to be superior to standard fixed-dose enoxaparin. Initiation of prophylaxis within 2 days of hospital admission was associated with a ~40% reduction in odds of DVT, but not PE.

In compliance with the guidelines of the Journal of Trauma, this work has not been published previously or submitted elsewhere. I, Sarah Lombardo, am a current member of EAST, an associate member of AAST, and a member-initiate of WTA. My contact information is included below. Thank you for your time and consideration.

A handwritten signature in black ink, appearing to read 'S Lombardo', with a stylized, cursive script.

Sarah Lombardo, MD. MSc.

University of Utah School of Medicine
Department of Surgery
30 N 1900 E
Salt Lake City, UT 84132

WEIGHT-BASED ENOXAPARIN THROMBOPROPHYLAXIS IN YOUNG TRAUMA PATIENTS: ANALYSIS OF THE CLOTT-1 REGISTRY

Introduction: Optimal venous thromboembolism (VTE) enoxaparin prophylaxis dosing remains elusive. Weight-based (WB) dosing safely increases anti-factor-Xa levels without the need for routine monitoring but it is unclear if it leads to lower VTE risk. We hypothesized that early (< 2 days) initiation of WB dosing would decrease VTE risk compared to standard fixed dosing (SFD).

Methods: Patients from the prospective, observational CLOTT-1 registry receiving prophylactic enoxaparin (n=5539) were categorized as WB (0.45-0.55 mg/kg BID) or SFD (30mg BID, 40mg qDay). Multivariate logistic regression was used to generate a predicted probability of VTE for WB and SFD patients.

Results: Of 4460 patients analyzed, 1082 (24.3%) were WB and 3378 (75.7%) were SFD. Mean age and Injury Severity Score were similar between groups but obesity was higher in the SFD cohort. Unadjusted VTE rates were comparable (WB 3.1% vs. SFD 4.0%; p=0.167). Early prophylaxis was associated with lower VTE rate (3.0% vs. 8.1%; p < 0.001) and DVT (2.1% vs. 7.2%; p < 0.001), but not PE (p = 0.175). After adjustment, VTE incidence did not differ by dosing strategy (aOR 0.84, 95% CI 0.51 – 1.37), however early administration was associated with a significant reduction in VTE (aOR 0.61, 95% CI 0.42 – 0.89).

Conclusion: WB prophylaxis in young trauma patients is not associated with reduced VTE rate when compared to SFD. The timing of the initiation of chemoprophylaxis may be more important than the dosing strategy. Further studies need to reconcile this disconnect across a wider age and comorbidity spectrum.

Level of Evidence: Level IV, therapeutic/care management

Keywords: venous thromboembolism, VTE prophylaxis, weight-based prophylaxis, enoxaparin

Complete manuscript title: Weight-based enoxaparin thromboprophylaxis in young trauma patients: analysis of the CLOTT-1 registry

Short title: Weight-based enoxaparin thromboprophylaxis

Authors: Sarah R. Lombardo, MD MSc¹; Marta L. McCrum, MD MPH¹; M. Margaret Knudson, MD²; Ernest E. Moore, MD³; Lucy Z. Kornblith, MD²; Amy M. Shui⁴, MA; Scott Brakenridge, MD^{5,6}; Brandon R. Bruns, MD^{7,8}; Mark D. Cipolle, MD^{9,10}; Todd W. Costantini, MD¹¹; Bruce A. Crookes, MD¹²; Elliot R. Haut, MD¹³; Andrew J. Kerwin, MD^{14,15}; Laszlo N. Kiraly, MD¹⁶; Lisa M. Knowlton, MD¹⁷; Matthew J. Martin, MD¹⁸; Michelle K. McNutt, MD¹⁹; David J. Milia, MD²⁰; Alicia Mohr, MD⁵; Frederick B. Rogers, MD²¹; Thomas M. Scalea, MD⁷; Sherry L. Sixta, MD⁹; David A. Spain, MD¹⁷; Charles E. Wade, PhD¹⁹; George C. Velmahos, MD²²; Ram Nirula, MD¹; Jade Nunez, MD¹

¹Department of Surgery, University of Utah, Salt Lake City

²Department of Surgery, University of California, San Francisco

³Department of Surgery, University of Colorado, Denver

⁴Department of Epidemiology and Biostatistics, University of California, San Francisco

⁵Department of Surgery, University of Florida, Gainesville

⁶now with Department of Surgery, University of Washington, Seattle

⁷Department of Surgery, University of Maryland, Baltimore

⁸now with Department of Surgery, University of Texas Southwestern, Dallas

⁹Department of Surgery, Christiana Health Care, Newark, Delaware

¹⁰now with Department of Surgery, Lehigh Valley Health, Allentown, Pennsylvania

¹¹Department of Surgery, University of California, San Diego

¹²Department of Surgery, Medical University of South Carolina, Charleston

¹³Department of Surgery, Johns Hopkins University, Baltimore, Maryland

¹⁴Department of Surgery, University of Florida, Jacksonville

¹⁵now with Department of Surgery, University of Tennessee, Memphis

¹⁶Department of Surgery, University of Oregon Health Sciences University, Portland

¹⁷Department of Surgery, Stanford University, Palo Alto, California

¹⁸Department of Surgery, Scripps Mercy Hospital, San Diego, California

¹⁹Department of Surgery, University of Texas, Houston

²⁰Department of Surgery, Medical College of Wisconsin, Milwaukee

²¹Department of Surgery, Lancaster General Hospital, Lancaster, Pennsylvania

²²Department of Surgery, Harvard University, Boston, Massachusetts

Contact information:

Sarah R. Lombardo, MD;
(correspondence)

Department of Surgery
University of Utah, SOM
30 N 1900 E
Salt Lake City, UT 84132

Ernest E. Moore, MD;
Lucy Z. Kornblith, MD;
Amy M. Shui, MA;
Scott Brakenridge, MD;

325 Ninth Ave, Box 359796
Seattle, WA 98104
5323 Harry Hines Blvd
Dallas, TX 75390
1240 S Cedar Crest Blvd
Suite 308

Brandon R. Bruns, MD;

Allentown, PA 18103

Mark D. Cipolle, MD;

Todd W. Costantini, MD;
Bruce A. Crookes, MD;
Elliot R. Haut, MD;
Andrew J. Kerwin, MD;
Laszlo N. Kiraly, MD;
Lisa M. Knowlton, MD;
Matthew J. Martin, MD;
Michelle K. McNutt, MD;
David J. Milia, MD;
Alicia Mohr, MD;
Frederick B. Rogers, MD;

Thomas M. Scalea, MD; 4755 Ogletown Stanton Rd
Sherry L. Sixta, MD; Newark, DE 19718

David A. Spain, MD;
Charles E. Wade, PhD;
George C. Velmahos, MD;
Ram Nirula, MD;
Jade Nunez, MD;

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Social media information: Early of initiation of VTE prophylaxis - not dosing strategy - is protective against posttraumatic DVT. @UofUSurgery #SurgTwitter #MedEd

Background

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially lethal complication after injury. Endothelial dysfunction resulting from trauma-induced local and systemic inflammatory signals significantly increases the risk of DVT and PE, even in baseline healthy individuals. Risk can be reduced through the use of mechanical and chemical VTE prophylaxis. A 2013 Cochrane database meta-analysis estimated the rate of DVT and PE in trauma patients receiving no prophylaxis at 8.7% and 3.3%, respectively. VTE prophylaxis of any kind (chemical, mechanical, or both) was associated with a significant reduction in both DVT (4.4%) and PE (1.7%).(1)

Enoxaparin is the preferred agent for chemoprophylaxis in severely injured patients without contraindications for low molecular weight heparin (LMWH), however controversy remains regarding optimal dosing strategies.(2-4) Early administration of LMWH has been associated with lower rates of DVT, PE, and in-hospital mortality when compared to unfractionated heparin (UH).(5-7) These studies typically used one of two fixed dosing regimens: 40 mg daily (qDay) or 30 mg every 12 hours (BID).(5, 8) Recent recognition that these regimens may not achieve adequate biochemical prophylaxis, as measured by anti-Xa activity level,(9, 10) has increased the support for alternative dosing strategies.(3) Obesity has been identified as a possible risk factor for subtherapeutic prophylaxis, leading to the adoption of weight-adjusted dosing schemes.(10, 11) Weight-adjusted enoxaparin prophylaxis is clearly linked to increased anti-Xa activity,(12, 13) but the anticipated benefit of reduced VTE rates remains to be seen. A recent systematic review of 45 studies evaluating the effect of standard fixed-dose (SFD) and weight-based (WB) chemoprophylaxis regimens on anti-Xa levels and VTE rates in obese trauma and surgical patients was unable to establish the superiority of a particular strategy.(14) Prior studies have been limited by small sample size, lack of appropriate control groups, and/or failure to correlate anti-Xa levels with clinical outcomes.(10, 12, 13, 15-17) The two main issues that remain unresolved regarding dosing of LMWH are whether achieving targeted anti-Xa levels translates into improved VTE related outcomes, and if a WB dosing strategy is superior to SFD strategies. If a WB strategy is superior to SFD dosing, then this may obviate the need for anti-Xa monitoring. At present, it remains unclear whether WB dosing of enoxaparin, when compared to SFD strategies, reduces posttraumatic VTE in at-risk individuals.

To address this question, we performed a secondary analysis of the Comparative Effectiveness Analysis of Venous Thromboembolism in Trauma Patients (CLOTT-1) data, a large prospective multicenter study, to evaluate the effectiveness of WB enoxaparin compared to SFD enoxaparin for posttraumatic VTE prophylaxis. We hypothesized that early initiation of WB dosing would be associated with a decreased risk of VTE when compared to patients receiving SFD enoxaparin prophylaxis.

Methods

CLOTT-1 population

The Consortium of Leaders in the study Of Traumatic Thromboembolism, phase 1 (CLOTT-1) was a multicenter, prospective, observational study of venous thromboembolism (VTE) following trauma. Trauma patients admitted to one of 17 participating American College of Surgeons (ACS) Level 1 trauma centers between January 1, 2018 and December 31, 2020 were screened for enrollment. Inclusion criteria included age 18 - 40 years, hospital length of stay (HLOS) ≥ 48 hours, and at least 1 posttraumatic risk factor for VTE, resulting in a final cohort of 7903 patients.(18)

Patient demographics and risk factors, height and weight, admission vitals, injury characteristics, laboratory values, measures of clinical care, and final disposition were extracted from the electronic medical record by participating sites and housed in the electronic data collection tool REDCap (Research Electronic Data Capture). Twelve posttraumatic risk factors for VTE were defined a priori: major head, chest or abdominal (Abbreviated Injury Score [AIS] ≥ 3) injury; spinal cord injury; pelvic fracture; lower extremity long bone fracture; major venous injury requiring repair; major operative procedure ≥ 1 hour and requiring general anesthesia; systolic blood pressure (SBP) < 90 mmHg; mechanical ventilation ≥ 4 days; femoral venous catheter; and presence of central line.

The type, dose, and date of initiation of pharmacologic VTE prophylaxis were extracted, along with dosing changes and missed doses. The data collection tool required that medication type and dosing for VTE prophylaxis was reported separately from medications and dosing intended for therapeutic anticoagulation. Any modification in dosing strategy (i.e. agent, dose, etc.) was captured along with the time, date, and the reason for the change. The total number of missed doses of pharmacologic prophylaxis were recorded for each patient. Each missed dose was also recorded individually, along with a time and date of the missed medication and the reported justification for holding the dose (e.g. patient refusal).

Research by the CLOTT study group is supported by a grant from the Defense Medical Research and Development Program, and managed by the National Trauma Institute and the Coalition for National Trauma Research (CNTR).

Study population and definitions

Patients from the CLOTT-1 registry receiving prophylactic enoxaparin during their hospital stay were identified (n=5539). Those with inferior vena cava (IVC) filter present at the time of admission or placed during the hospital course, HLOS < 3 days, or non-survivable injuries (defined as Injury Severity Score (ISS) of 75 or regional Abbreviated Injury Score (AIS) of 6) were excluded (Figure 1). Observations with missing values for height or weight were also excluded due to inability to calculate patient BMI. The lower and upper limits for BMI were set at 12 kg/m² and 200 kg/m², respectively. Patients were considered obese if BMI ≥ 30 kg/m².

Prophylactic dosing strategy was classified as either weight-based (WB; 0.45-0.55 mg/kg BID) or standard (SFD; 30mg BID or 40mg qDay). Patients weighing between 50 kg and 70 kg who received enoxaparin 30mg BID were assigned to WB because this is the appropriate WB dose for this weight range. Patients with non-standard, non-weight-based dosing were censored. Early prophylaxis was defined as receipt of first dose of VTE chemoprophylaxis within 2 days of hospital admission.

Statistical analysis

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4 The primary outcome was incidence of VTE. The secondary outcomes of interest were
5 incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), and rates of in-hospital
6 complications attributable to chemoprophylaxis, including worsening of intracranial hemorrhage,
7 solid organ bleeding, or other sites of new or worsened bleeding (i.e. wound, gastrointestinal,
8 genitourinary). Diagnosis of DVT and PE were confirmed by standard imaging techniques. The
9 date and results of extremity duplex ultrasonography and CT chest angiography during the
10 hospital course were recorded. As this was an observational study, no study protocol directed
11 the screening, prophylaxis, or treatment of patients with suspected VTE.
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14 The study was performed on an intention-to-treat basis, with the assignment of WB vs
15 SFD made based upon the first recorded dose of prophylactic enoxaparin. Univariate and
16 bivariate analysis used common statistical tests to compare WB and SFD populations. Mean and
17 standard deviation (SD) are reported for continuous variables with normal distribution, and
18 differences compared using the independent samples t-test. Nonparametric variables are
19 summarized by median and interquartile range (IQR), and evaluated using the Wilcoxon rank
20 sum test. Categorical variables are reported as percentages and compared using Chi-squared test
21 or Fisher's exact test, as appropriate.
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24 Multivariate logistic regression models for VTE, DVT, and PE were developed to explore
25 the effect of weight-based enoxaparin dosing, after adjusting for known risk factors. All
26 potential risk factors that were significant at $p < 0.2$ were entered into a forward stepwise logistic
27 regression model. Variables retained in the final models are reported in Table 3, along with
28 model diagnostics, including area under the receiver operator curve (AUC) and Hosmer-
29 Lemeshow goodness-of-fit (GOF) testing. Hospital site was included to control for variations in
30 clinical practice, but are not included in the summary table. Adjusted odds ratios (aOR) and 95%
31 confidence intervals (CI) are reported.
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34 A substantial number of patients received a non-WB, non-SFD enoxaparin for
35 chemoprophylaxis (n=454, 9.2%). While these observations were censored for the primary
36 analysis, upon closer review of the data we noted that 85.0% of this censored cohort received 40
37 mg BID. Recent publications have advocated for higher empiric doses of enoxaparin in trauma
38 patients with moderate or greater risk for VTE and no contraindications to LMWH [Ley 2020]
39 As such, we completed two additional analyses in which patients receiving 40 mg BID were
40 classified as WB if (1) reported patient weight was < 50 kg (n=60), which represented over-
41 weight based dosing, or (2) reported patient weight was ≥ 70 kg (n=278), consistent with a
42 weight-stratified approach. The results of these sensitivity analyses did not alter our findings, the
43 details of which can be found in the supplement (Tables S1-2).
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46 Power calculations were completed using a range of incidence rates obtained from
47 published studies, as well as limited data on the patient population used in this study. The
48 purpose of this calculation was to assist in our interpretation of the results, and not to direct the
49 analytic strategy. Previously reported VTE rates in trauma patients have ranged widely; the
50 highest rates are typically among severely injured patients with multiple VTE risk factors and in
51 studies utilizing routine VTE surveillance practices.(5, 13) As such, we performed several power
52 calculations with sensitivity analysis to account for this known variation. The expected VTE rate
53 for SFD enoxaparin dosing was evaluated at 4%, 7%, 12%, and 20%.(11, 13, 14) The
54 hypothesized reduction in VTE with WB dosing was tested at 15%, 30% and 50%, based upon
55 reported effects of WB dosing strategies on both anti-Xa levels and VTE rates.(11, 15, 19) The
56 type 1 error was set at 0.05, and power at 0.80. The 1:3 ratio of WB to SFD patients was used in
57 these calculations based upon the observed ratio from initial review of this data. The results of
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the analysis are included in the supplement (Table S3). Based upon this evaluation, this study is powered to detect a 30% difference in VTE rate between treatment groups assuming a baseline VTE rate of at least 12% in the SFD group.

Data was cleaned and analyzed using the statistical package Stata for Mac, Version 16.1 (StataCorp, College Station, TX). Investigational Review Board (IRB) approval was obtained individually at each site contributing to the CLOTT-1 registry, and separate IRB approval was obtained at the University of Utah for this analysis. The data collection and initial analysis of the CLOTT-1 registry was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Defense Medical Research and Development Program under award W81XWH-17-1-0673. There is no additional funding to report for this secondary analysis. This manuscript was drafted in accordance with the Strengthening and Reporting of Observational studies in Epidemiology (STROBE) checklist for retrospective observational studies (Table S4).

Results

Study Population

Of the 7903 patients captured in the CLOTT study, 5539 received prophylactic dosing of enoxaparin during their admission. 625 patients met exclusion criteria (Figure 1), and 454 patients were further excluded due to non-standard dosing. The final cohort consisted of 4460 patients: 1082 (24.3%) received WB and 3378 (75.7%) received SFD enoxaparin DVT chemoprophylaxis.

WB patients were younger, more likely to be female, and less likely to be obese (Table 1). Mean ISS was statistically higher for the WB cohort. With respect to the 12 predefined VTE risk factors, groups were comparable except head AIS ≥ 3 , major operation, major venous injury, and central line, all of which were more common in the WB group.

Enoxaparin dosing

The majority of patients (78.3%) in the WB group received 30 mg BID (Table 2). In the SFD group 68.2% of patients received 30 mg BID and 31.8% 40 mg qDay. The first dose of chemoprophylaxis was administered within 2 days of admission for the majority of patients (WB 80.6% vs. SFD 81.9%). Changes to dosing regimens occurred in 13.8% of the WB group and 16.3% of the SFD group. There were 4319 reported missed doses among 1968 patients (mean 2.2, range 1- 26), with a higher rate of missed doses in the WB group (44.4% vs. 39.4%). The most common reason for missed doses were IR or OR procedure and patient refusal, which was more frequent in the WB group ($p=0.010$; Table 2). Concern for bleeding or bleed-related complications were less commonly cited justifications, and did not differ by prophylaxis strategy. There was a higher rate of reported regimen changes in the SFD group ($p=0.045$), but most patients (86.2% for WB and 83.7% for SFD) did not have alterations in chemoprophylaxis agent or dose.

Unadjusted outcomes

The composite VTE rate for the study population was 3.7% ($n = 167$; DVT 2.9%, PE 1.2%). VTE incidence was 3.1% ($n = 33$; DVT 2.5%, PE 1.0%) in the WB group and 4.0% ($n =$

134; DVT 3.1%, PE 1.2%) in the SFD group, which did not differ significantly ($p = 0.167$) (Figure 2). Early prophylaxis was associated with significantly lower rates of VTE ($2.8\% \leq 2$ days vs. $8.1\% > 2$ days, $p < 0.001$) and DVT (2.0% vs. 7.1% , $p < 0.001$), but not PE (1.0% vs. 1.7% , $p = 0.110$) (Figure 2 and Table S5). VTE and DVT were more common among obese patients, however these differences were only statistically significant among obese patients receiving WB dosing.

Complications attributable to chemoprophylaxis were uncommon. Enoxaparin exposure was associated with progression of intracranial hemorrhage in 9 patients (0.2%), and worsening or new solid organ bleeding in 4 patients (0.1%). Overall, there was a 1.1% rate of chemoprophylaxis-associated complication within this cohort, and no difference was detected between groups (Table S5).

Adjusted outcomes

After adjustment, VTE, DVT, and PE rates did not differ by dosing strategy (Table 3). For all outcomes, RBC transfusion volume, presence of central venous catheter, and prolonged mechanical ventilation were significant positive predictors. Conversely, the variable for missed doses of VTE prophylaxis did not meet prespecified inclusion criteria for any model and was omitted for all outcomes. Early initiation of chemoprophylaxis was associated with a 40% reduction in the likelihood of VTE (aOR 0.61 , 95% CI $0.41 - 0.89$). This is attributable to a reduction in the odds of DVT (aOR 0.58 , 95% CI $0.37 - 0.89$), as there was no significant effect on odds of PE.

Discussion

The results of our study showed no difference in efficacy of WB versus SFD enoxaparin for VTE prophylaxis in young trauma patients. However, early initiation of prophylaxis was protective against VTE regardless of dosing strategy. This appears to be driven by decreased incidence of DVT, but not PE. Other significant risk factors for VTE within this cohort include increased age, obesity, more severe injury (higher ISS, RBC transfusion volume), and 6 of the 12 predefined VTE risk factors (severe chest injury, lower extremity long bone fracture, spinal cord injury, presence of femoral or other central line, and prolonged mechanical ventilation). Interestingly, missed doses of VTE chemoprophylaxis were more common among the WB cohort, but were not independently predictive of worse clinical outcomes.

Effective prophylaxis against posttraumatic VTE with LMWH may not be dose-dependent. Subtherapeutic anti-Xa activity is common among patients receiving traditional dosing regimens, and has been associated with an elevated risk for VTE.(9, 10) New strategies seeking to improve these outcomes include use of higher fixed doses (ie. 40 mg BID),(3) weight-based or weight-stratified dosing,(13, 15) and enoxaparin dosing titrated to anti-Xa activity level.(17, 19) A shared characteristic of all non-traditional dosing schemes is that most patients ultimately receive larger doses of LMWH. While higher doses do result in a greater percentage of patients achieving biochemical prophylaxis targets by anti-Xa activity level,(11) no single strategy has been proven to lower the risk of posttraumatic VTE relative to traditional dosing.(14) Our evaluation of the CLOTT-1 database offers the largest prospective assessment of weight-based LMWH dosing strategies for VTE prophylaxis in a trauma population. The

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4 absence of anti-Xa levels in this dataset precluded biochemical assessment of adequate
5 prophylaxis. However, the lack of evidence to support anti-Xa as an accurate measure of VTE
6 prophylaxis highlights the importance of reporting upon clinically relevant events. Our null
7 result is consistent with the conclusions of several recent reviews that found insufficient
8 evidence to back the adoption of non-traditional dosing strategies to achieve the clinical goal of
9 reducing posttraumatic VTE risk.(4, 20)
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12 Unlike the controversy surrounding dosing strategies, early initiation of
13 chemoprophylaxis clearly decreases the risk of VTE after trauma.(21) A 2020 evaluation of >
14 79,000 patients from the Michigan Trauma Quality Improvement Program database used
15 multivariate logistic modeling to optimize the comparison of patients receiving their first dose of
16 VTE prophylaxis < 24 hours, 24 to < 48 hours, and $\geq$ 48 hours after hospital admission.(22)
17 Delays in prophylaxis were associated with increased VTE risk relative to the earliest group (<
18 24 hour). Patients receiving their first dose $\geq$ 48 hours from admission had a greater than two-
19 fold increased risk of VTE (OR 2.35, $p < 0.001$). Similarly, we found early initiation of
20 prophylaxis to confer a 40% risk reduction in VTE, with the protective benefit persisting
21 regardless of dosing strategy. The 2020 MTQIP study did not exclude patients who received UH,
22 but did adjust for the type of pharmacologic agent, finding LMWH to be superior to UH with
23 respect to VTE risk (OR 0.62, $p < 0.001$). (22) Taken together, these findings suggest that both
24 agent and timing may be more important than dosing scheme alone. The low rate of bleeding
25 complications was anticipated based upon existing literature, and again highlights the safety of
26 early LMWH in trauma populations.(21, 23) Our results reinforce current guidelines
27 recommending prophylaxis be started as soon as possible for stable patients without
28 contraindications.(3, 4)
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34 Recently, the correlation between posttraumatic DVT and pulmonary clots has been
35 called into question.(24-26) The primary analysis of the CLOTT-1 data sought to characterize
36 posttraumatic pulmonary thrombosis (PT) as an entity that is clinically distinct from DVT and
37 PE.(18) Supported by their findings that patients with PT have specific injury patterns and
38 clinical risk factors, the authors raise intriguing questions as to the ability of posttraumatic VTE
39 prophylaxis to prevent such events. Of the 157 patients with PE on chest imaging, 117 (74.5%)
40 had no evidence of DVT and were thus classified as PT.(18) If a similar proportion of PE-
41 positive patients in our sub-analysis are assumed to in fact have PT, we can interpret the lack of
42 effect of early prophylaxis in our risk-adjusted model for PE as further evidence that the
43 pathophysiology of PT is distinct from DVT and PE. As such, future investigations evaluating
44 the effects of VTE prophylaxis should aim to differ between PE and PT when defining
45 clinical outcomes.
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49 *Limitations*

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51 This study has limitations that are inherent to its observational nature and may limit broad
52 generalizability of our findings. Patients included in this analysis are relatively young and lack
53 many of the comorbidities and risk factors common among older trauma populations. Obesity
54 was relatively uncommon in the WB group. This precluded sub-analysis of this important group
55 of patients, who were most likely to benefit from higher enoxaparin dosing. Variability in
56 institutional practices with respect to VTE prophylaxis and DVT screening are likely significant
57 across the 17 contributing centers. We attempted to control for the effects of unmeasured site-
58 specific difference in our adjusted analysis. Due to the absence of anti-Xa activity data, we were
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unable to assess dosing strategy or clinical events with respect to this commonly reported measure. Most importantly, we recognized that 85% of patients that did not classify as either WB or SFD received enoxaparin 40 mg BID, an increasingly common fixed prophylactic dose promoted by Western Trauma Association's 2020 guidelines.(3) As such, we performed two additional *post hoc* analyses that considered these patients to have received WB enoxaparin if their weight was (1) < 50 kg (over-dosed) or (2) ≥ 70 kg (weight-stratified). The results of this additional work did not alter our conclusions and are included in the supplement. Finally, despite this being the largest prospective evaluation of weight-based VTE prophylaxis in trauma yet published, due to the low baseline incidence of VTE in patients receiving SFD enoxaparin we may have been underpowered to detect any small incremental benefit that WB dosing might afford.

Conclusion

We found no difference in rates of VTE between weight-based vs standard dosing strategy in a young trauma population. Early administration had a significant effect, associated with 40% reduction in odds of VTE. Both dosing strategies appear to be safe, with comparably low risks of bleed progression. Obesity is a known risk factor for VTE, however the relationship between higher body mass, posttraumatic physiology, and VTE risk is poorly understood. Further studies are needed to evaluate the risk-benefit profile of LMWH dosing strategies in older and obese trauma populations, while paying close attention to timing of prophylaxis initiation and other known VTE risk factors.

Author contributions:

Literature search: Lombardo, Nunez

Study design: Lombardo, Nirula, Nunez

Data collection and original study design: Knudson, Kornblith, Shui, Brakenridge, Bruns, Cipolle, Costantini, Crookes, Haut, Kerwin, Kiraly, Knowlton, Martin, McNutt, Milia, Mohr, Rogers, Sixta, Spain, Wade, Nirula.

Data analysis: Lombardo

Data interpretation: Lombardo, McCrum, Nunez, Nirula

Writing: Lombardo, Nunez

Critical revision: Lombardo, McCrum, Nunez, Nirula

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Table 1: Patient demographics and VTE risk factors

	Weight-based (n = 1082)	Standard (n = 3378)	p-value
Age (years; mean, SD)	28 (7)	29 (6)	<0.001
Female [^]	35.7%	23.7%	< 0.001
Race/Ethnicity [^]			0.006
Caucasian	40.7%	45.3%	
African American	32.1%	31.1%	
Latinx	17.4%	13.6%	
Other	9.8%	9.9%	
Obesity (BMI $\geq$ 30 kg/m ²)	3.1%	30.3%	<0.001
PMHx [^]			
VTE	0.8%	0.7%	0.685*
Cancer	0.1%	0.3%	0.468*
Blunt mechanism [^]	74.7%	75.5%	0.583
ISS (mean, SD) [^]	18 (11)	17 (11)	0.002
VTE risk factors			
Head AIS $\geq$ 3	26.9%	23.6%	0.026
Chest AIS $\geq$ 3	32.2%	30.5%	0.309
Abdomen AIS $\geq$ 3	23.8%	21.7%	0.134
Spinal cord injury	4.4%	3.7%	0.275
Pelvic fx	21.6%	20.1%	0.279
Lower ext long bone fx	35.9%	37.0%	0.497
Major venous repair	6.1%	4.5%	0.034
Major operation	81.2%	73.9%	<0.001
SBP < 90 mmHg	7.0%	6.2%	0.345
Ventilator > 4 days	12.6%	10.5%	0.052
Femoral venous catheter	6.1%	4.7%	0.062

Central line	11.3%	9.1%	0.034
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* Fisher's exact test

^ Missingness: Female n = 1; Race/ethnicity n = 12; Hx VTE n = 20; Hx cancer n = 16;
Mechanism n = 2; ISS n = 83

Table 2 - Prophylactic enoxaparin dosing

	Weight-based (n = 1082)	Standard (n = 3378)	p-value
Initial dosing			
40 mg Qday	n/a	31.8%	
20 mg BID	0.2%	n/a	
30 mg BID	78.3%	68.2%	
40 mg BID	20.4%	n/a	
50 mg BID	0.9%	n/a	
60 mg BID	0.1%	n/a	
Early prophylaxis (≤ 2 days)	80.6%	81.9%	0.318
Missed doses			
Any missed dose	44.4%	39.4%	0.003
Median (IQR) number of missed doses among those missing any dose	2 (1, 3)	2 (1, 3)	0.586*
Reasons for missing doses (among those with any missed dose)			
IR/OR procedure	47.2%	42.6%	0.010
Patient refusal	36.4%	39.1%	0.121
Bleeding concern	5.8%	4.7%	0.169
Bleeding complication	1.5%	1.0%	0.197
Regimen changes			
Any regimen change	13.8%	16.3%	0.045
Median (IQR) number of dosing changes among those with any change	1 (1, 2)	1 (1, 1)	0.324*
Medication type change (among those with any change)	39.7%	33.0%	0.079

* Wilcoxon Rank Sum test

IQR = Interquartile range

Table 3: Multivariable logistic regression model of VTE, DVT, and PE rates. Hospital sites in model, but not reported here. Omitted values (--) indicate variables that were not retained in the final stepwise model.

	VTE	DVT	PE
Model diagnostics			
Observations (n)	4277	4277	4091
AUC	0.864	0.880	0.855
Hosmer-Lemeshow GOF	0.491	0.812	0.817
Variables: aOR (95% CI)			
Weight-based dosing	0.84 (0.51, 1.37)	1.01 (0.57, 1.78)	0.74 (0.35, 1.57)
Age	1.03 (1.00, 1.06)	1.03 (1.00, 1.07)	--
Obesity	1.57 (1.05, 2.34)	1.43 (0.91, 2.27)	1.73 (0.89, 3.37)
ISS	1.02 (1.00, 1.04)	1.02 (0.99, 1.04)	1.03 (1.01, 1.06)
Medicare/Medicaid	0.69, (0.46, 1.03)	--	0.58 (0.28, 1.21)
Hispanic/Latinx	--	1.64 (1.01, 2.67)	--
Hx cancer	--	4.68 (0.55, 40.00)	--
Early prophylaxis (≤ 2 days)	0.61 (0.41, 0.89)	0.58 (0.37, 0.89)	--
RBC transfusions	1.06 (1.03, 1.09)	1.06 (1.03, 1.09)	1.06 (1.02, 1.09)
Blunt mechanism	0.60 (0.38, 0.93)	0.68 (0.42, 1.11)	--
TXA	--	1.76 (0.96, 3.21)	--
VTE risk factors			
Head AIS ≥ 3	--	--	0.43 (0.20, 0.92)
Chest AIS ≥ 3	1.59 (1.07, 2.35)	1.66 (1.07, 2.59)	--
Shock on admission	--	0.64 (0.33, 1.22)	--
Lower extremity long bone fracture	1.51 (1.03, 2.21)	--	1.57 (0.87, 2.85)
Spinal cord injury	1.87 (1.00, 3.50)	--	3.19 (1.23, 8.26)

Central venous catheter	2.78 (1.77, 4.39)	2.90 (1.71, 4.92)	2.67 (1.30, 5.49)
Femoral catheter	2.29 (1.38, 3.80)	3.01 (1.66, 5.46)	--
Prolonged mechanical ventilation (≥ 4 days)	1.87 (1.15, 3.05)	1.94 (1.10, 3.42)	2.31 (1.04, 5.12)

Figure 1

Figure 1: Flow diagram

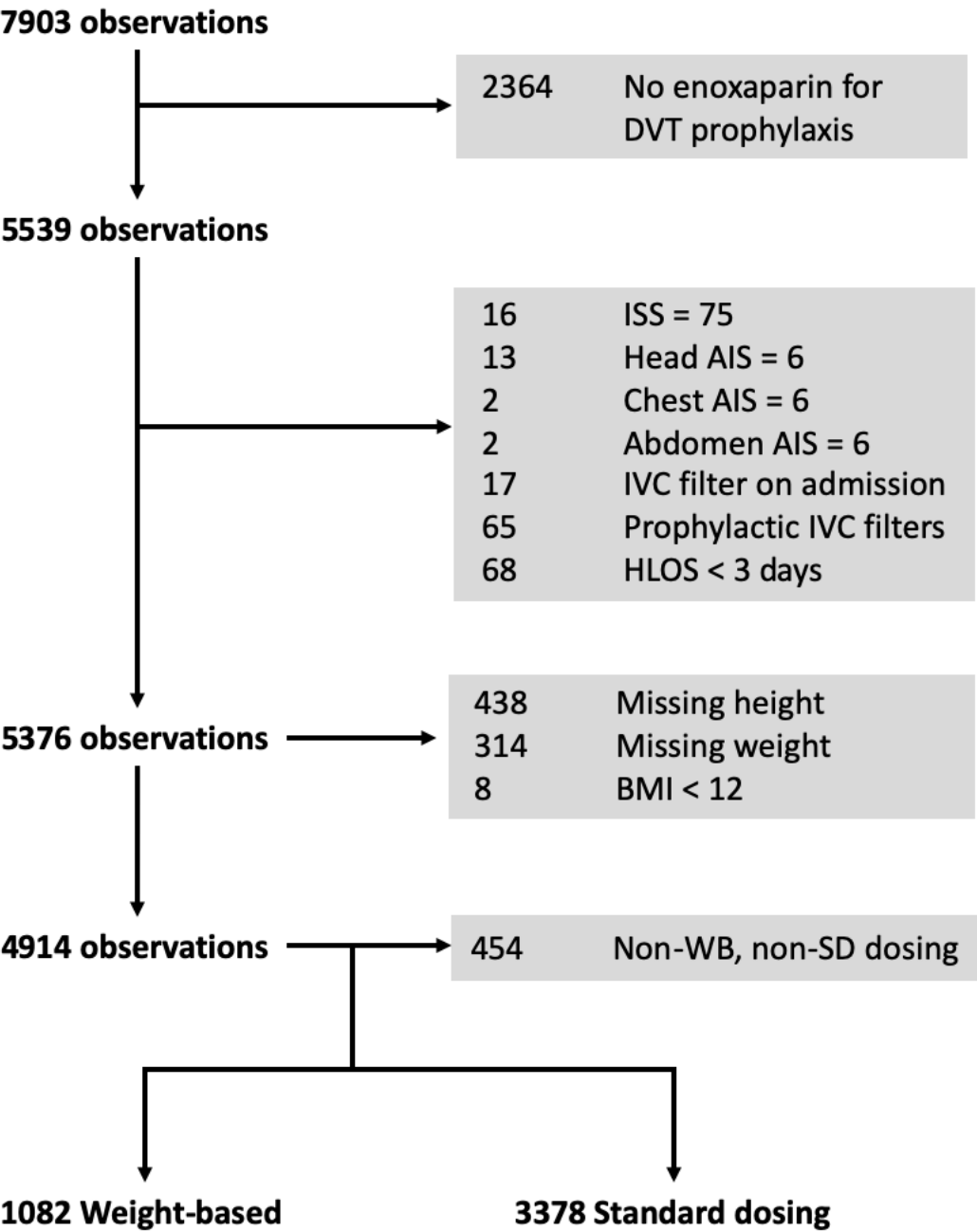
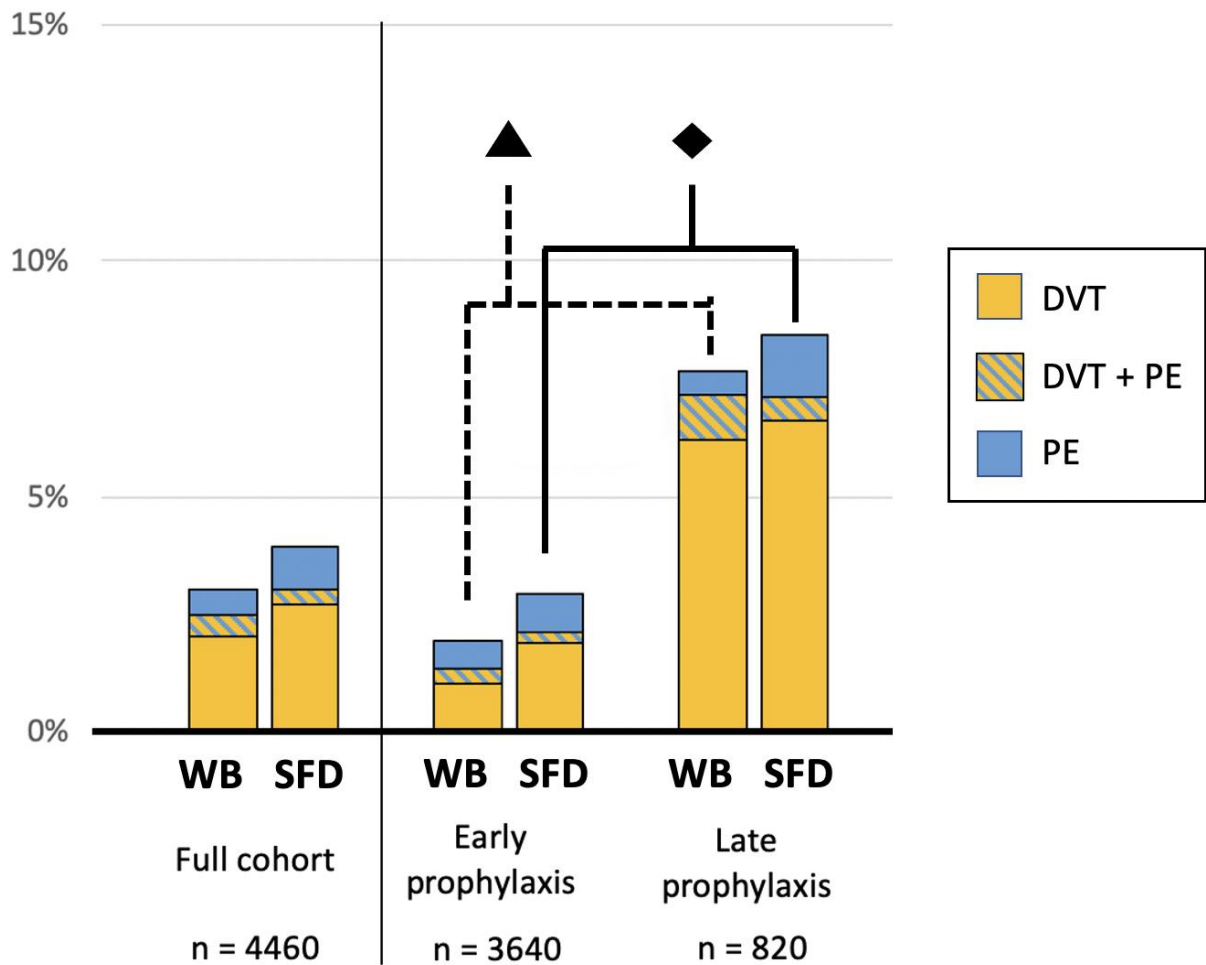
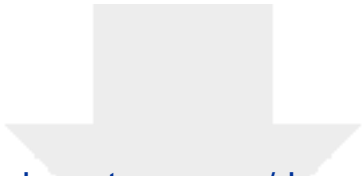


Figure 2

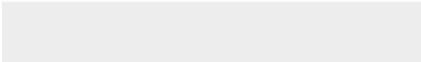
Figure 2: Unadjusted VTE, DVT, and PE rates by cohort. Early prophylaxis was associated with significantly lower rates of VTE and DVT relative to delayed initiation of prophylaxis for both WB (▲) and SFD (◆) groups.





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Supplemental Data File (.doc, .tif, pdf, etc.)
Supplemental tables.docx



The Pathogenesis of Post-Traumatic Pulmonary Thrombosis: Etiology, Risk Factors, and Implications for Treatment

M Margaret Knudson, Eugene E Moore for the CLOTT Study Group

Background: Pulmonary thrombi (PT) are detected with increasing frequency on chest CT scans despite concerted efforts aimed at deep venous thrombosis (DVT) prevention. We hypothesized that post-traumatic PT are unrelated to DVT and associated with independent and identifiable risk factors including chest trauma.

Methods: CLOTT is a prospective, Department of Defense funded, observational study conducted at 17 level 1 trauma centers designed specifically to investigate post-traumatic PT. The study includes all trauma patients aged 18-40 years admitted for a minimum of 48 hours with at least one identifiable trauma-associated venous thromboembolism (VTE) risk factor. Data was collected on a unique comprehensive case report form (CRF) and entered into a secure central electronic data base.

Results: Over a 3-year period (2017-2020) 7880 patients were enrolled with a mean age of 29 years (74% male, 76 % blunt mechanism of injury). 277 patients were diagnosed with DVT, 40 with both DVT and PT and 117 with isolated PT (overall incidence 4% DVT; 2% PT). In those with PT, 24% were evident on the CT of the chest obtained on admission. Post-traumatic risk factors **independently associated** with the development of PT but not DVT include the presence of shock (BP<90 mm Hg) on admission (OR 2.74, 95% CI 1.72-4.39, $p<0.0001$); chest injury of AIS $\geq$ 3 (OR 1.72, 95% CI 1.16-2.56, $p=0.007$), which was present in 53% of patients with PT, and the use of twice daily heparin as prophylaxis (OR 3.26, 95% CI 1.27-8.35, $p=0.01$).

Conclusion: To our knowledge, this CLOTT study is the largest prospective investigation in the world focusing on post-traumatic pulmonary thrombosis. From it, we conclude that post-traumatic PT are not embolic but rather result from a combination of trauma induced coagulation disorders and post-injury inflammatory response. These findings have major implications for VTE prevention, treatment, and quality metrics. Additional studies should focus on the safety of observation versus treatment of asymptomatic post-injury PT.

FIBRINOLYTIC SHUTDOWN IS AN EARLY PREDICTOR OF POST-TRAUMATIC VTE: A PROSPECTIVE STUDY FROM THE CLOTT-2 RESEARCH GROUP

Background: VTE remains a frequent post-injury complication despite pharmacological prophylaxis. Fibrinolysis shutdown (FS) has been proposed as a potential contributing cause. We hypothesized that a tPA-challenge thromboelastography (TPA-TEG) suggestive of FS early after major injury would predict VTE events.

Methods: A subgroup of adults (n=103) enrolled in the CLOTT2 5-center prospective study had tPA-TEG obtained at 12- and 24-hours post-ICU admission. VTE was diagnosed by duplex screening or clinically ordered pulmonary embolism imaging. The predictive performance of TPA-TEG was assessed by areas under the receiver-operating characteristics curve (AUC). These AUCs were compared to standard TEG maximum amplitude (MA), the VTE Risk Assessment Profile (RAP) and the Trauma Embolic Scoring System (TESS). The Youden Index was used to define optimal cutoffs for these variables.

Results: Overall VTE incidence was 16.8%(n=17); 14 DVT, 4 PE, 1 both. Compared to those without VTE, VTE patients were more severely injured (ISS=34 vs 22, p=0.002) and had higher RAP (12 vs 10, p=0.004). TESS was not significantly different (7 vs 5, p=0.20). The tPA-TEG LY30 at 12 hours showed the largest AUC, followed by the RAP(Table). tPA-resistant patients had 3.8 increased odds of developing VTE, while patients with RAP>11 had 4.3 increased VTE odds. However, as the RAP score calculation requires data not available at 12 hours, FS emerges as the most accurate early predictor of VTE events.

Conclusion: This study has important implications for both the timing of initiation and the choice of agent used for post-traumatic VTE prophylaxis.

Table: Area under the receiver operating characteristics curve for predictors of VTE in descending order of magnitude

	Area	95% Wald Confidence Limits	
tPA challenge TEG LY30 at 12HRS	0.7225	0.5790	0.8661
RAP	0.7208	0.6074	0.8341
TEG LY30 at 12HRS	0.6556	0.5056	0.8055
TEG LY30 24HRS	0.6042	0.4770	0.7314
TESS	0.5992	0.4430	0.7554
MA 24HRS	0.5854	0.4202	0.7506
MA 12HRS	0.5415	0.3765	0.7065
tPA challenge LY30 24HRS	0.5124	0.3459	0.6789

TISSUE PLASMINOGEN ACTIVATOR RESISTANCE IS AN EARLY PREDICTOR OF POST-TRAUMATIC VENOUS THROMBOEMBOLISM: A PROSPECTIVE STUDY FROM THE CLOTT RESEARCH GROUP

Background: Venous thromboembolism (VTE) remains a frequent post-injury complication despite pharmacological prophylaxis. We hypothesized that patients at high risk for VTE would exhibit early dysregulation of fibrinolysis as measured by kaolin TEG and specialized TEG assays with tissue plasminogen activator added (tPA-TEG).

Methods: A subgroup of patients enrolled in the CLOTT-2, multi-center prospective study had kaolin TEG and tPA-TEG data at 12- and 24- hours post admission. Patients underwent a screening duplex venous ultrasound exam during the first week unless clot was already detected on computed tomography. Injury factors associated with early fibrinolysis shutdown (SD) (defined as kaolin TEG Ly30% $\leq$ 0.3%) and tPA resistance (tPA-R) (defined as kaolin TEG with tPA 75ng Ly30% $<$ 2.1%) were investigated as was the association of the TEG measurements with the development of VTE.

Results: 141 patients had both TEG measurements at 24 hours and 135 had both at 12 hours. SD was evident at 12 hours in 71/135 (52.6%) of patients and in 62/141 (44%) at 24 hours. tPA-R was found in 61/135 (45.2%) at 12 hours and in 49/141 (34.3%) at 24 hours. Factors significantly associated with SD included receiving > 4 units of FFP in the first 24 hours, the presence of a major brain injury or pelvic fracture and the need for major surgery. In contrast, factors significantly associated with early tPA-R included > 4 units of RBCs transfused in the first 24 hours, and the presence of a major chest injury or long bone fracture. DVT was detected in 15 patients and pulmonary clots in 5 (overall VTE rate 14.2%). tPA-R at 12 hours was found to be an independent risk factor for VTE (hazard ratio 5.57, 95% CI 1.39-22.39).

Conclusions: These findings of early dysregulated fibrinolysis have implications for both the timing of initiation and choice of agent used for post-traumatic VTE prophylaxis.

Level of Evidence: II

Study Type: Original Research/Therapeutic

Keywords: VTE, TEG, Fibrinolysis shutdown, tPA resistance

TISSUE PLASMINOGEN ACTIVATOR RESISTANCE IS AN EARLY PREDICTOR OF
POST-TRAUMATIC VENOUS THROMBOEMBOLISM: A PROSPECTIVE STUDY FROM
THE CLOTT RESEARCH GROUP

Short title: Tissue Plasminogen Activator Resistance and VTE

Authors and Affiliations: M. Margaret Knudson MD

Department of Surgery, University of California San Francisco

Peggy.Knudson@ucsf.edu

Hunter B. Moore MD

Department of Surgery, University of Colorado

Hunter. Moore@cuanschutz.edu

Ernest E. Moore MD

Department of Surgery, EE Moore Shock Trauma Center

Denver Health

Ernest.Moore@dhha.edu

Lucy Z. Kornblith MD

Department of Surgery, University of California San Francisco

Lucy.Kornblith@ucsf.edu

Lazlo N. Kiraly MD

Department of Surgery, Oregon Health Science University

kiraly@ohsu.edu

Michelle K. McNutt MD

Department of Surgery, U. Of Texas Medical Center, Houston

Michelle.K.McNutt@uth.tmc.edu

Charles E. Wade PhD

Department of Surgery, U. of Texas Medical Centers, Houston

Charles.E.Wade@uth.tmc.edu

Brandon R. Bruns MD

Department of Surgery, U. Texas Southwestern

Brandon.Bruns@UTSouthwestern.edu

Angela Sauaia MD, PhD

School of Public Health, U. Colorado Denver

Angela.Sauaia@cuanschutz.edu

Corresponding Author: M. Margaret Knudson MD Department of Surgery, SFGH

1001 Potrero Avenue Ward 3A; San Francisco CA 94110

Phone: 628-206-4626; FAX: 628-206-5484

Peggy.Knudson@ucsf.edu

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BACKGROUND

Trauma induced coagulopathy has been recognized for decades and remains a common cause of hemorrhagic shock and death after major injury.¹⁻³ More recently, with increased use of thromboelastography (TEG) in trauma patients, an exaggerated hypercoagulable condition termed fibrinolysis shutdown has been observed frequently on admission with an associated mortality of 22%.⁴⁻⁶ Fibrinolysis shutdown (SD) can be further classified by TEG analysis into those patients lacking hypersensitivity to tissue plasminogen activator (tPA resistant).⁷ Patients who exhibit tPA resistance (tPA-R) have a 5-fold higher incidence of death compared to patients without fibrinolysis shutdown.⁷ While the association between a hypercoagulable state and the development of venous thromboembolism (VTE) has been suggested, no large-scale prospective study focusing specifically on fibrinolysis shutdown, tPA resistance and VTE after injury has been conducted.^{8,9}

The CLOTT research group (Consortium of Leaders in the study Of Traumatic Thromboembolism) was funded by the Department of Defense to conduct prospective, multi-center studies on post-traumatic pulmonary clots. Our first study (CLOTT-1) included data on 7880 injured patients and demonstrated that most early pulmonary clots are primary pulmonary thrombi and not embolic.¹⁰ CLOTT-2 contains a subset of those patients who were the most critically injured and required Intensive Care Unit (ICU) care. We hypothesized that we could identify patterns of injury associated with early SD and tPA-R among enrolled patients. We further sought to determine if early SD or tPA-R could predict the development of VTE.

METHODS

Study Design and Data Collection

CLOTT-1 was a prospective, multicenter observational cohort study conducted over a period of two years (2018-2020) at 17 major trauma centers in the US.¹⁰ A comprehensive electronic case report form was designed exclusively for the study and research coordinators received training on data collection prior to the start of the study. Periodic quality checks were performed by the Principal Investigator (MMK) and the data was entered into the secure central Research Electronic Data Capture (REDCap) system at the University of California San Francisco.

Patients were screened for inclusion in CLOTT-1 if they were admitted to any of the 17 participating trauma centers and had at least one of our previously identified risk factors for VTE.¹¹ These risk factors included: shock on admission (systolic blood pressure < 90 mmHg); major head injury (AIS $\geq$ 3); major chest injury (AIS $\geq$ 3); major abdominal injury (AIS $\geq$ 3); pelvic fracture; long bone fracture (lower extremity above the ankle); a major named venous injury requiring ligation or repair; the need for major surgery on admission (surgery lasting at least 1 hour and requiring general anesthesia) and the presence of coagulopathy on admission (international normalized ratio > 1.5). Additional data collected included the use of blood products during the first 24 hours, prophylactic measures utilized, missed doses of anticoagulants, imaging procedures related to DVT and pulmonary clots, VTE events, treatment of VTE including complications related to treatment, injuries identified, and outcomes. **Note:** because these studies were funded by the Department of Defense, only patients in the deployable age range (18-40 yrs.) were eligible for inclusion,

Patients enrolled in CLOTT-1 were also eligible for inclusion in CLOTT-2 if they were severely injured and required at least 48 hours of ICU care. CLOTT-2 investigators have active coagulation laboratories and included the following 5 institutions: the University of California, San Francisco and the Zuckerberg San Francisco General Hospital, the Ernest E. Moore Shock Trauma Center at Denver Health and the University of Colorado, Oregon Health Sciences University, the University of Maryland, and the University of Texas Health Science Center, Houston. Enrollment into CLOTT-2 required signed consent by the patient or their surrogate and the study was approved by each of the 5 institutional review boards as well by the US Department of Defense Human Research Protection Office (HRPO). Realizing the difficulty in obtaining prompt consent from severely injured (or unidentified) patients or their surrogates, and the minimal risk to the patients, the IRBs and HRPO allowed a short period of waiver of consent in order for the study to be as inclusive as possible. CLOTT-2 patients had serial blood samples collected for TEG analysis within 6-12 hours of admission and then at 24, 36 and 48 hours and again on days 5 and 7. Each patient underwent a duplex venous ultrasound exam for DVT at day 3, unless prior imaging had identified DVT or pulmonary clots that required treatment. The primary outcome of interest for CLOTT-2 was the development of a hypercoagulable state by TEG assays and its association with VTE. Secondary outcomes included the trauma-related factors associated with fibrinolysis shutdown (SD) and/or tPA resistance (tPA-R) as defined below.

TEG Assays

Citrated Kaolin TEG: Blood was collected in 3 ml citrated blood tubes at as many of the time intervals described above as possible. Samples were kept at room temperature and assayed within 2 hours after the blood draw in accordance with manufacturer's recommendations. Kaolin

TEG assays were run according to the manufacturer's instructions on the TEG 5000 Thrombelastograph Hemostatis Analyzer (Haemonetics, Braintree MA). The following variables were recorded from the tracing of the TEG: R time (minutes), angle (degrees), maximum amplitude (MA mm) and lysis 30 minutes after MA (Ly30%), **For the purposes of this study, fibrinolysis shutdown (SD) was defined at kaolin TEG Ly30% $\leq$.3%. This definition was derived as predictive of mortality from studies of 1000 patients at the Ernest E. Moore Shock Trauma Center (unpublished data).**

tPA Challenge TEG: The research coordinators from the other four centers were trained in person in Denver to correctly perform tPA Challenge TEGs developed by the University of Colorado trauma research group (HGM, EEM, AS).^{7,12} Paired samples collected at the same time as the citrated kaolin TEG were analyzed. Human single chain tPA (Molecular Innovation, Novi MI) was diluted in 5% bovine serum albumin in phosphate buffered saline to a final concentration of 10 $\mu\text{g}/\text{ul}$. Individual aliquots of tPA (prepared for a final concentration of 75 ng/mL) were stored at -80 degrees C and thawed immediately before use. From the sample collected from the patient, 500 μl of whole blood was pipetted into a customized vial containing the tPA and mixed by gentle inversion. A 340 μl aliquot of this mixture was then transferred to a 37 degree C TEG cap preloaded with 20 μl of 0.2 mol/L CaCl_2 and analyzed on the same TEG 5000 machine. **For the purposes of this study, tPA resistance (tPA-R) was defined as Ly30% < 2.1%. derived from data at the Ernest E. Moore Shock Trauma Center (unpublished data).** Residual plasma from these blood samples were stored at -80 degrees C for later analysis as described in the discussion below.

Statistical Methods

All analyses were conducted in SAS vs 9.4 (SAS Institute, Cary NC). Unadjusted comparisons used Chi-square, Fisher's Exact or Wilcoxon rank sum test for independent samples as appropriate. Competing risk analysis was used for assessing risk factors for VTE censoring for death and discharge or missing samples. Generalized linear models or linear mixed models were used to evaluate temporal trends of categorical or continuous variables respectively. Statistical significance was set to $p < 0.05$. There were no adjustments for multiple outcomes, as all study outcomes were pre-specified hypotheses, in order to avoid increased type II errors.^{13,14} This manuscript was prepared in accordance with the Strengthening and Reporting of Observational studies in Epidemiology (STOBE) checklist.

RESULTS

Two hundred forty patients were enrolled in CLOTT-2: 80% male, 80% resulting from blunt trauma, with a median age of 29 years. Although most patients had several blood samples for analysis during the first week, a preliminary look at the data suggested that the signal for an association between VTE, SD, and/or tPA-R was strongest during the first 24 hours post injury (data not shown). We also recognized that most severely injured ICU patients would be receiving chemical prophylaxis after the first 24 hours which might affect our TEG measurements. Additionally, most VTE events were occurring during the first 4 days (likely somewhat related to the surveillance duplex exams performed as part of the research study). Therefore, we first chose to concentrate on the patients with paired blood samples collected during the first 24 hours post injury. This included 141 patents with paired samples at 24 hours and 135 with paired samples at 12 hours post injury. The VTE rate in these 141 patients was 14.2% (15 DVT, 5 Pulmonary clots). **Table 1** contains the data for the 12-hour samples which were available for 135 patients.

At 12 hours 71/135 (52.8%) met the definition of SD and 38 of those 71 (53.5%) also demonstrated tPA-R versus only 23/64 (35.9%) of those without SD ($p=0.04$). At 12 hours, a total of 61/135 (45.2%) met the definition of tPA-R and 38 of the 61 (62.3%) also showed SD versus 33/74 (44.8%) of those without tPA-R ($p=0.04$). At 24 hours, 62/141 (44.0%) patients had SD and of these patients 30/62 (48.8%) also had SD at 12 hours. Similarly, of the 49/141 (34.8%) who had tPA-R at 24 hours, 61.2% had tPA-R at 12 hours.

We next investigated the trauma related factors associated with the development of SD or tPA-R at 12 and/or 24 hours. The data on all 240 patients who had at least one sample for analysis within the first 24-hour period and the association between the risk factors and the development of SD or tPA-R is shown in **Table 2**. In the final adjusted analysis, we used only the data from patients who had paired samples at both 12 and 24 hours. As can be seen in **Table 3**, the adjusted relative risk (RR) for development of SD at 12 hours was significant in patients who received > 4 units of FFP on the day of admission ($RR=1.04$, $p < .0001$). At 24 hours, SD was independently associated with traumatic brain injury (TBI), ($RR=1.73$, $p=0.0007$), pelvic fracture ($RR=1.39$, $p<.0001$) and the need for major surgery as defined above ($RR=2.37$, $p<0.001$). In contrast, tPA-R at 12 hours was associated with the need for > 4 units of red blood cell (RBC) transfusions in the first 24 hours ($RR=1.03$, $p=0.03$), the presence of a major chest injury ($RR=1.47$, $p=0.02$), and a long bone fracture ($RR=1.79$, $p<0.001$). At 24 hours both long bone fracture and the need for RBC transfusion remained significant for their association with tPA-R. (**Table 4**)

Finally, competitive risk models were developed in order to examine the independent association between early tPA-R, SD and the development of VTE (**Table 5**) Of note, 73.5% of these patients had either SD or tPA-R prior to development of VTE. As can be seen in the final unadjusted analysis (**Table 5**) tPA-R at 12 hours emerged as an independent significant risk

factor for the development of VTE when adjusted for other injury-related risk factors listed in Table 2.

DISCUSSION

One of the most feared consequences of severe traumatic injury is the development of trauma induced coagulopathy. Seminal work by Brohi and others documented a 46% mortality among patients who were coagulopathic after injury versus only 10.9% among those without clotting abnormalities.¹ Coagulopathy after trauma is related to injury severity and the presence of hypoperfusion resulting in death from hemorrhage.^{1,3} In fact, recognition of failure to maintain hemostatic clot (acute fibrinolysis) in trauma patients led to the interest in the administration of tranexamic acid (TXA) in the prehospital setting in both military and civilian patients.^{15,16}

On the other end of the spectrum, failure to lyse clot after injury has received less attention. The first work in trauma demonstrating fibrinolysis activation with subsequent shutdown was from Innes and Sevitt in 1964, with subsequent work from the Netherlands terming this “fibrinolytic shutdown” following myocardial infarction and after trauma.^{17,18} These investigators and others described a rapidly developing pattern of fast-acting inhibitor of tissue-type plasminogen activator after trauma leading to fibrinolysis shutdown.^{18,19} Higher levels of plasminogen-activator inhibitor-one (PAI-1) have also been detected in the plasma of patients who developed venous thromboembolism after total hip surgery compared to those without VTE.²⁰ More recently fibrinolysis shutdown has been correlated with thromboembolic events in patients with severe coronavirus disease (COVID-19) and the recognition that the inflammation associated with this disease leads to both macro-and micro-clots in the arterial as well as the venous system.²¹⁻²⁴ Collectively this work prompted the large-scale, multi-national research projects by the

National Institute of Health focusing on the use of anticoagulants in patients with COVID-19 infections.^{22,23}

The current ubiquitous use of thromboelastography in trauma resuscitation has greatly facilitated the study of fibrinolysis shutdown (SD). Most of the pioneering work in this area has been led by the investigators in Denver (including authors HBM, EEM and AS) focusing on both the underlying mechanistic pathology as well as the clinical implications of SD after injury. In a seminal paper, these authors described three distinct fibrinolysis phenotypes identified in a series of trauma patients based on TEG analysis: physiologic fibrinolysis (Ly30 0.9-2.0%), hyperfibrinolysis (Ly30 > 3%) and fibrinolysis shutdown (Ly30 < 0.8%).⁶ **Note: The definition of SD has been redefined by these authors consistent with the Ly30 $\leq$ 0.3% used in the current study.** In that study, the mortality rate among those with physiologic fibrinolysis was (3%) compared with 44% in the hyperfibrinolysis group and 17% in patients with SD.⁶ In a multicenter evaluation of 2,540 severely injured patients (Injury Severity Score > 15) SD was the most commonly observed phenotype.⁵ The odds ratio of death in those patients with hyperfibrinolysis was highest (odds ratio 3.3 95% CI 2.4-4.6, $p < 0.0001$) but was also elevated in patients with SD (odds ratio 1.6 95% CI 1.3-2.1, $p = 0.0003$) compared to those with physiologic fibrinolysis. Investigations by these authors documented a five-fold increase in mortality in trauma patients who lacked hypersensitivity to tissue plasminogen activator (tPA-R).⁷ Utilizing ELISA assays, they demonstrated that SD was associated with the activity of tissue plasminogen activator inhibitor-1 (PAI-1) which blocks the conversion of plasminogen to plasmin and thus prevents the breakdown of fibrinogen to fibrin split products during clot lysis.²⁵

Other investigators have contributed to our understanding of SD. Meizoso and others reported that persistent SD (lasting for one week) was an independent predictor of mortality with an odds

ratio of death as high as 8.48 (95% CI 1.35-53.18, $p=0.022$).⁵ In their study, the authors found that highest rates of SD in patients with penetrating injuries and those receiving blood product transfusions. Animal models suggest that the severity of SD is associated with the degree of tissue injury.²⁶

Platelets have been shown to not only be contributors to clot formation but also central to regulation of clot lysis.²⁷⁻²⁹ Specifically, platelets release PAI-1 in parallel with the endothelium. A secondary analysis of data from the PROPPR study group suggested that platelet dysfunction and suppressed clot lysis contributed to the development of VTE after injury.³⁰ Given the role of platelets in both clot formation and lysis, the use of antiplatelet drugs for VTE prevention deserves further investigation especially in patients with SD. A retrospective study by Brill and others found that pre-injury aspirin use was associated with lower VTE rates after injury when combined with in-hospital heparinoid prophylaxis.³¹

Our study has documented that approximately half of critically injured patients have SD or tPA-R (or both) as early as 12 hours post injury. In a smaller bi-institutional study evaluating clot risk in trauma patients with blunt solid organ injury, low fibrinolytic activity was also associated with clot complications at 12 hours, while clot strength was associated with thrombotic complications 48 hours after admission.³² In contrast, another study evaluating TEG and stroke from blunt cerebral vascular injury did not find an association with prolonged clot lysis (Ly30) but there was an association with clot strength measured by MA on TEG analysis.³³ It is possible that vascular beds in various anatomical positions differ in their responses to risk factors for thrombotic events.

In our study, those most at risk for the development of a very early (12 hours post injury) hypercoagulable state are those who require transfusions and patients with chest trauma or long

bone fractures. At 24 hours, brain injuries, pelvic fractures and those undergoing major surgery during the first 24 hours are most at risk for displaying SD or tPA-R. A review of the data in Tables 2,3 and 4 would suggest that transfusions of RBCs, plasma, platelets, and cryoprecipitate could be implicated as causative factors contributing to the inability to lyse clot. Perioperative blood transfusions have been associated with post-operative VTE in other fields of surgery with an estimated odds ratio of 2.95.^{34,35} It has been proposed that transfused blood acts as a modulator of the inflammatory cascade and thus contributes to hypercoagulation. A previous study in trauma patients by Schultz et al found that patients who had been transfused with RBCs had over three times the risk of developing VTE compared to those without transfusions although the number of units of blood is not mentioned in that study³⁶. Gearhart and others also found that transfusion of > 4 units of RBCs conferred a significant risk of developing VTE.³⁷ However, it is unclear whether it is the RBCs themselves (or FFP as we have shown here) that contribute to the hypercoagulable state or that these transfusions merely reflect the severity of shock and tissue injury that drives the hypercoagulability.

We have demonstrated that a hypercoagulable state as defined by tPA-R is an independent predictor of the development of VTE. While we don't anticipate that every trauma center will immediately begin testing patients for tPA resistant clot, recognizing the injury-related risk factors for developing an early hypercoagulable state as shown in Tables 3 and 4 can inform the timing of initiation of prophylactic measures in those most at risk.

Our study has several limitations. While we intended to obtain blood samples at multiple intervals throughout the first week of admission, many samples were missed. Discharge from the ICU or hospital before the 7 day blood draw accounted for many missed samples. Not all centers had 24/7 research staff to collect samples and perform the TEG assays. Research was also

impacted by the COVID-19 pandemic during which many research projects were curtailed or completely suspended. Another limitation is the age range of our enrolled patients (18-40) which questions the generalization to older trauma patients. Additional research from CLOTT will focus on patients with delayed development of a hypercoagulable state (after the first 24 hours), on patients who resolve this state but redevelop it again (observed anecdotally) and on associations with platelet biology. The plasma samples stored from these patients are currently being analyzed for tPA, PAI-1, tPA/PAI-1, plasminogen, plasmin-antiplasmin (PAP), thrombin activated fibrinolysis inhibitor (TAFI), clotting factor XIII and biomarkers that may provide further insight into the biological mechanisms of post-traumatic clotting disorders. Given the potential contribution of platelets to the inability to lyse clot, the addition of aspirin as a prophylactic agent deserves further attention.

Despite these limitations, this study contributes to our understanding of clotting disorders following major injury. The recognition that a hypercoagulable state develops within 12 hours of injury suggests that perhaps it is not the failure of our prophylactic measures to prevent VTE but rather our failure to provide them when they are most needed.

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Author Contributions:

Study Design: Knudson, E.Moore, Kornblith, Wade, Bruns, Kiraly, McNutt,

H. Moore, Sauaia

Data Acquisition: Knudson, E Moore, Kiraly, Wade, McNutt, Bruns

Interpretation of Data: Knudson, E Moore, H Moore, Kornblith, Sauaia

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Table 1: Number and Percent of Patients Demonstrating Fibrinolysis Shutdown (FD) and tPA Resistance (tPA-R) among 135 patients at 12 hours post-admission

	12 hours tPA Resistance	12 hours tPA Resistance	
12 hours fibrinolysis shutdown	NO	YES	Total
NO	41 (64.1%)	23 (35.9%)	64 (47.4%)
YES	33 (46.5%)	38 (53.5%)	71 (52.6%)
Total	74 (54.8%)	61 (45.2%)	135 (100%)

p=0.04 denoting significant differences between the columns

SD (+): Meets criteria for Fibrinolysis Shutdown (kaolin TEG Ly30% $\leq$ 0.3%)

SD (-): Does not meet criteria for Fibrinolysis Shutdown

tPA-R (+): Meets criteria for tPA Resistance (kaolin TEG with tPA 75ng Ly30% < 2.1%)

tPA-R: Does not meet criteria for tPA-R

Table 2: Trauma Related Factors Associated with Early Fibrinolytic Shutdown (FD) and tPA Resistance (tPA-R)

Factor	No SD or tPA-R in 1 st 24 hrs. n=41/179 (22.9%)	SD at 12 hours n=84/169 (49.7%)	tPA-R at 12 hours n=61/135 (45.2%)	SD at 24 hours n=76/180 (42.2%)	tPA-R at 24 hours n=49/141 (34.8%)
Shock n=35/240	6/30 (20.0%)	9/23 (39.1%)	12/20 (60.0%)	11/25 (44.0%)	12/24 (50.0%)
TBI n=123/240	19/92 (20.7%)	48/89 (53.9%)	26/70 (37.1%)	47/94 (50.0%)	27/73 (37.0%)
Spinal cord injury n=14/240	3/11 (27.3%)	5/10 (50.0%)	5/10 (50.0%)	4/10 (40.0%)	2/8 (25.0%)
Chest injury n=119/240	15/83 (18.1%)	48/82 (58.5%)	35/62 (56.5%)	45/86 (52.3%)	27/63 (42.9%)
Abdominal injury n=85/240	13/69 (18.8%)	30/55 (54.6%)	27/48 (56.3%)	31/67 (46.3%)	24/56 (42.9%)
Pelvic fracture n=65/240	10/53 (18.9%)	25/40 (62.5%)	21/34 (61.8%)	29/54 (53.7%)	20/47 (42.6%)
Long bone fracture n=69/240	6/56 (10.7%)	29/49 (59.2%)	28/43 (65.1%)	29/56 (51.8%)	25/49 (51.0%)
Venous injury n=29/240	4/21 (19.1%)	9/16 (56.3%)	7/12 (58.3%)	11/23 (47.8%)	6/17 (35.3%)
RBCs > 4 units in 1 st 24 hrs. n=48/240	3/37 (8.1%)	15/26 (57.7%)	17/22 (77.3%)	19/33 (57.6%)	19/28 (67.9%)
Plasma > 4 units in 1 st 24 hrs. n=47/240	3/36 (8.3%)	17/26 (65.4%)	17/22 (77.3%)	19/33 (57.6%)	20/27 (74.1%)
Platelets > 2 units in 1 st 24 hrs. n=17/240	1/12 (8.3%)	6/11 (54.6%)	6/8 (75%)	7/10 (70.0%)	5/7 (71.4%)
Cryo > 2 units in 1 st 24 hrs n=7/240	1/6 (16.7%)	1/1 (100%)	1/1 (100%)	2/3 (66.7%)	3/3 (100%)
Major surgery first day n=185/240	29/141 (20.6%)	65/121 (53.7%)	50/103 (48.5%)	66/133 (49.6%)	42/107 (39.3%)

Note: The definitions for each of these trauma-related factors are contained in the methods section of the manuscript with n=number with each factor. In the other columns the numerator represents the number negative or positive for SD or tPA-R over the total number of samples obtained at that time period for patients with that particular factor. Cryo=cyroprecipitate.

Table 3: Independent injury-related risk factors for the development of fibrinolysis shutdown (SD) at 12 and 24 hours

Time Period	Variable	Relative Risk	Lower Confidence limits (95%)	Upper Confidence limits (95%)	P-value
SD at 12 hours	Plasma > 4 units in 1 st 24hrs.	1.04	1.03	1.06	<.0001
	Shock (< 90 mm Hg)**	0.61	0.38	0.98	0.94
SD at 24 hours	TBI	1.71	1.25	2.34	0.0007
	Pelvic fracture	1.39	1.23	1.56	<.0001
	Major surgery 1 st day	2.37	2.20	2.55	<.0001

TBI=Traumatic Brain Injury with AIS $\geq$ 3

*Note: Shock is associated with hyperfibrinolysis not SD⁸

Table 4: Independent injury-related risk factors for development of tPA-R at 12 and 24 hours

Time Period	Variable	Relative Risk	Lower Confidence Limits (95%)	Upper Confidence Limits (95%)	p-value
12 hours	RBCs>4/first 24 hours	1.036	1.003	1.07	0.03
	Chest injury	1.47	1.08	2.02	0.02
	Long bone fx	1.79	1.50	2.13	<.0001
24 hours	RBCs>4 first 24 hours	1.03	1.02	1.05	<.0001
	Long bone fx	1.80	1.20	2.68	0.0045

Fx=fracture

Table 5: Independent Hazard Ratios of SD and tPA-R at 12 and 24 hours for the development of VTE (adjusted for VTE risk factors)¹¹

Parameter	Hazard Ratio	Lower 95% Confidence Limits	Upper 95% Confidence Limits
SD at 12 hours	1.29	0.4990	3.403
tPA-R at 12 hours*	5.57	1.391	22.39
SD at 24 hours	0.57	0.22	1.46
tPA-R at 24 hours	1.821	0.600	5.543

*statistically significant risk factor (p<0.05)