Trauma Surgery & Acute Care Open

Addition of aspirin to venous thromboembolism chemoprophylaxis safely decreases venous thromboembolism rates in trauma patients

Daniel Lammers ,[1] Michelle Scerbo,[2] Annamaria Davidson,[2] Matthew Pommerening,[2] Jeffrey Tomasek,[2] Charles E Wade,[2] Jessica Cardenas,[2] Jan Jansen ,[1] Charles C Miller,[2] John B Holcomb[1]

[1]Division of Trauma and Acute Care Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA
[2]Surgery/Center for Injury Research, The University of Texas Health Science Center McGovern School of Medicine, Houston, Texas, USA

Correspondence to
Dr Daniel Lammers; dtlammer@gmail.com

Received 26 March 2023
Accepted 3 October 2023

To cite: Lammers D, Scerbo M, Davidson A, *et al*. *Trauma Surg Acute Care Open* 2023;**8**:e001140.

ABSTRACT

Background Trauma patients exhibit a multifactorial hypercoagulable state and have increased risk of venous thromboembolism (VTE). Despite early and aggressive chemoprophylaxis (CP) with various heparin compounds ("standard" CP; sCP), VTE rates remain high. In high-quality studies, aspirin has been shown to decrease VTE in postoperative elective surgical and orthopedic trauma patients. We hypothesized that inhibiting platelet function with aspirin as an adjunct to sCP would reduce the risk of VTE in trauma patients.

Methods We performed a retrospective observational study of prospectively collected data from all adult patients admitted to an American College of Surgeons Level I Trauma center from January 2012 to June 2015 to evaluate the addition of aspirin (sCP+A) to sCP regimens for VTE mitigation. Cox proportional hazard models were used to assess the potential benefit of adjunctive aspirin for symptomatic VTE incidence.

Results 10,532 patients, median age 44 (IQR 28 to 62), 68% male, 89% blunt mechanism of injury, with a median Injury Severity Score (ISS) of 12 (IQR 9 to 19), were included in the study. 8646 (82%) of patients received only sCP, whereas 1886 (18%) patients received sCP+A. The sCP+A cohort displayed a higher median ISS compared with sCP (13 vs 11; p<0.01). The overall median time of sCP initiation was hospital day 1 (IQR 0.8 to 2) and the median day for aspirin initiation was hospital day 3 (IQR 1 to 6) for the sCP+A cohort. 353 patients (3.4%) developed symptomatic VTE. Aspirin administration was independently associated with a decreased relative hazard of VTE (HR 0.57; 95% CI 0.36 to 0.88; p=0.01). There were no increased bleeding or wound complications associated with sCP+A (point estimate 1.23, 95% CI 0.68 to 2.2, p=0.50).

Conclusion In this large trauma cohort, adjunctive aspirin was independently associated with a significant reduction in VTE and may represent a potential strategy to safely mitigate VTE risk in trauma patients. Further prospective studies evaluating the addition of aspirin to heparinoid-based VTE chemoprophylaxis regimens should be sought.

Level of evidence Level III/therapeutic.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The rate of venous thromboembolism (VTE) events in trauma patients remains persistently high despite many years of research aimed at optimizing VTE prophylaxis strategies within this high-risk patient population.

WHAT THIS STUDY ADDS

⇒ The addition of aspirin to standard VTE chemoprophylaxis strategies may reduce the rate of VTE within trauma patients by inhibiting platelet function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings offer a novel approach for VTE chemoprophylaxis and should be explored prospectively prior to routine incorporation.

BACKGROUND

Venous thromboembolism (VTE), to include both deep venous thrombosis (DVT) and pulmonary embolism (PE), represents a potential major cause of morbidity and mortality experienced by trauma patients after their initial injury.[1–3] Despite extensive efforts designed to mitigate the risk of VTE development, a wide degree of variability in practice patterns persist.[4 5] VTE chemoprophylaxis within the traumatically injured patient population is widely accepted as the standard of care; however, multidisciplinary opinions on the optimal medication regimen, dosing, and timing of initiation are controversial within individual medical specialties involved.

Although traumatic bleeding initially results in the consumption of coagulation factors, impaired platelet function, and hyperfibrinolysis, a rebound hypercoagulable state subsequently predominates following successful hemorrhage control and resuscitation that is characterized by supraphysiologic levels of thrombin and fibrinogen which predisposes critically injured trauma patients for increased risk of VTE.[6–9] Current chemoprophylaxis regimens largely target the inhibition of thrombin, which in turn reduces the functional capacity of the plasma-based coagulation cascade and thrombin-induced platelet activation. Despite this, ongoing platelet activation through alternative pathways is hypothesized to play a critical role in post-injury VTE formation.[10–13] Viscoelastic testing parameters in post-injury patients have demonstrated hypercoagulable states that may be resistant to standard low molecular weight heparin (LMWH)-based regimens

and suggest that platelets may represent the dominant contributing factor for overall clot strength.[10 13] This theory is further supported by a growing body of evidence that suggests that VTE rates are not affected by alterations in LMWH dosing strategies based on anti-Xa activity.[14–16] Further complicating the picture, the classic teaching that PE in trauma patients arise from DVT has been challenged as recent evidence suggests a large cohort of pulmonary clots are secondary to primary pulmonary thrombosis. This phenomenon demonstrates a different set of associated risk factors than traditionally taught and may benefit from alternative chemoprophylactic management strategies.[17 18]

Aspirin, an oral antiplatelet agent, has demonstrated efficacy in VTE prevention within the medical and orthopedic literature.[19–22] Recently, the use of aspirin as a sole prophylactic agent has been shown to be non-inferior to LMWH for VTE prophylaxis in isolated orthopedic trauma patients, highlighting the potential benefit of its use within this specific population; however, the role of antiplatelet medications for VTE prophylaxis in polytrauma patients remains largely understudied.[23 24] Due to the complex nature of post-injury clot formation, along with the continued high rates of post-injury VTE despite longstanding and intensive efforts with LMWH chemoprophylaxis, we sought to assess the addition of platelet inhibition to decrease the rates of VTE formation. We hypothesized that incorporating aspirin to traditional VTE chemoprophylaxis regimens would decrease the risk of developing VTE after traumatic injury.

METHODS

Study setting and selection of participants

Approval of this study was obtained by the local Institutional Review Board prior to initiation of this review. Institutional University Health System Consortium (UHC) Database and the institutional trauma registry were queried to identify all patients admitted to the trauma service at a single American College of Surgeons verified Level 1 trauma center between January 2012 and June 2015. All adult patients (age ≥16 years old) who sustained a traumatic injury and were admitted to the trauma service per institutional policy were included in the study.

Patients were excluded if a VTE was present on admission (POA), were either discharged or died prior to receiving standard chemoprophylaxis, or were initially started on therapeutic dosing for known VTE or history of VTE requiring full anticoagulation. The UHC Database was further used to identify all trauma patients that had a charge code for aspirin and prophylactic or therapeutic LMWH or unfractionated heparin (UFH). Additionally, the institutional pharmacy database was queried to identify the dose and duration of administration of all heparinoids (LMWH or UFH) and aspirin. Patients who received standard VTE chemoprophylaxis (sCP) regimens were compared with those who received sCP and aspirin (sCP+A) in efforts to identify an association between the addition of aspirin and decreased VTE rates. The study protocol was performed and reported per The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[25]

Definitions

sCP, in accordance with the institutional guidelines in place at the time of this study, was defined as either prophylactic dose of subcutaneous enoxaparin (30 mg every 12 hours or 40 mg every 12 hours if weight >150 kg) or subcutaneous heparin (5000 units every 8 hours or 7500 units every 12 hours if weight >150 kg). VTE prophylaxis was initiated at the earliest time possible after exclusion traumatic brain or spine injury, where initiation was governed by the discretion of the appropriate consulting service. Routine use of adjunctive aspirin was not standardized per institutional guidelines during the study period. Presence of VTE was investigated after the development of clinical symptoms (new or unilateral leg or arm swelling or pain, shortness of breath, increased rate of breathing, decreased oxygen saturation, chest pain, or increased heart rate). Diagnosis of PE was confirmed via helical computed tomography angiogram, high-probability ventilation-perfusion scan, autopsy, or clinical context with echocardiogram showing right heart strain. Diagnosis of DVT was confirmed via ultrasonography. DVT found in both upper and lower extremities were included; however, they were separately analyzed after data collection. Below-knee thrombosis was not included unless the clot burden was found to extend into the popliteal, femoral, or iliac veins. Routine screening for DVT was not conducted during any part of the study period.

Risk of VTE was estimated by using the Trauma Embolic Scoring System (TESS). This score has been previously validated from the National Trauma Data Bank, with a score of 6 or greater (range 0–14) predicting VTE in trauma patients with a sensitivity of 82% and specificity of 84%, as well as a sensitivity and negative predictive value over 97% in high-risk populations.[26 27] Variables within the model include age, Injury Severity Score (ISS), obesity (defined as a body mass index (BMI) >30 kg/m^2), prolonged ventilation (greater than 3 days), and a lower extremity fracture.[26]

Bleeding complications were recorded within the Trauma Registry by criteria defined by the American College of Surgeons Committee on Trauma.

Outcomes

The primary outcome was a symptomatic VTE diagnosed during hospitalization. Secondary outcomes assessed for bleeding complications.

Statistical analysis

Univariate analysis was conducted to compare demographic and injury data between patients receiving sCP or sCP+A. Nonparametric continuous variables were expressed as median values with the 25th and 75th percentile ranges. Comparisons between groups were performed using the Wilcoxon rank-sum (Mann-Whitney U test). Categorical data were reported as proportions and, where appropriate, tested for significance using χ^2 or Fisher's exact tests. The potential benefit of adding aspirin for symptomatic VTE prevention was assessed by Cox proportional hazards model after adjusting for the dose of heparinoid, major venous repair, and TESS. Bleeding complications were assessed after adjusting for known risks for these complications: blood transfusion, central venous catheter, prolonged operative time, cardiovascular disease, sCP, and any dose of aspirin. Statistical significance was defined by a p value <0.05. All statistical analyses were performed using STATA Statistical software (V.13.1, College Station, TX) or SAS software V.9.2 (SAS Institute Inc. Cary, NC).

RESULTS

Patient demographics

total of hen, figure 1 represents a flow diagram of the study population. The 2662 patients that did not receive sCP and did not have a VTE POA were either discharged (88%) or died (12%) within a median of 1 (1, 2) day of admission.

Table 1 demonstrates the demographic, injury, and VTE risk factors of the patients that received sCP compared with sCP+A.

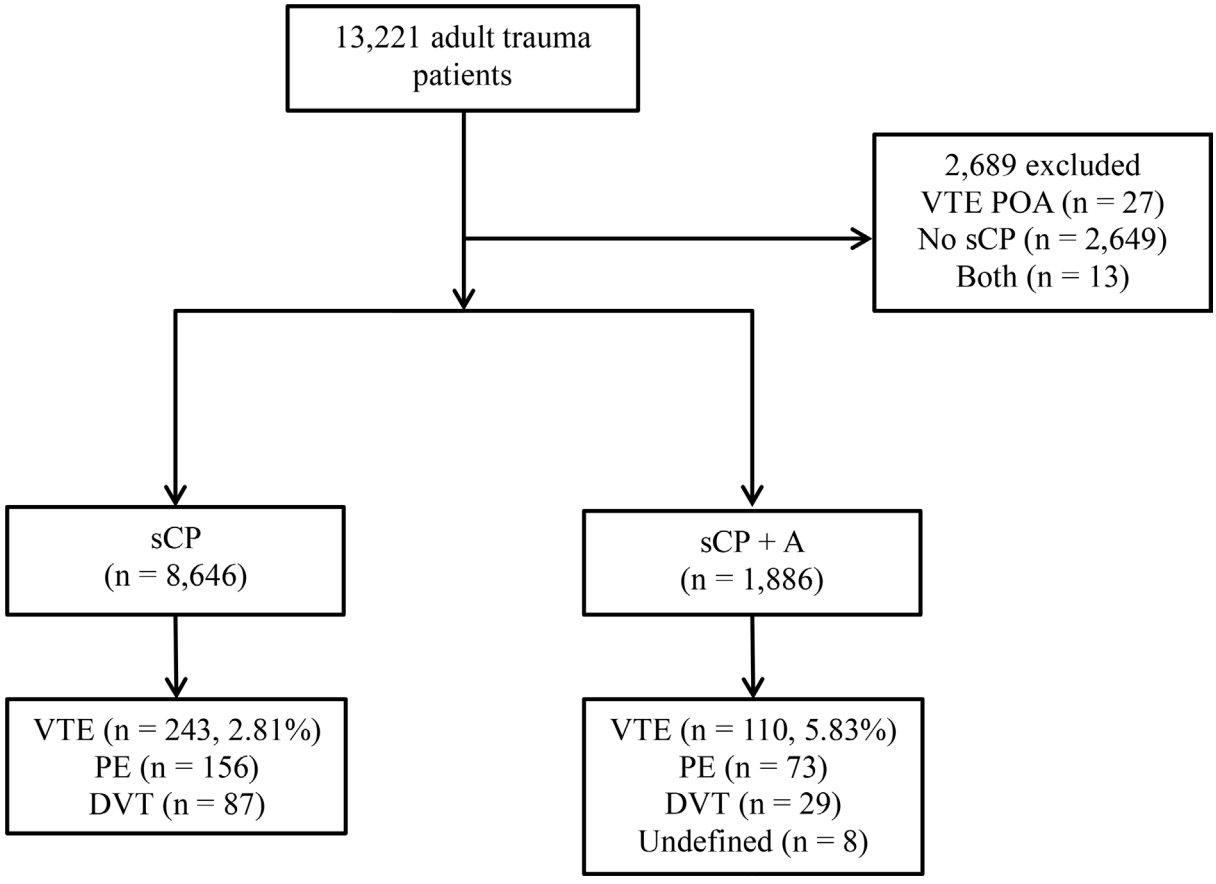

Figure 1 Flow diagram of subjects included within the study. DVT, deep venous thrombosis; PE, pulmonary embolism; POA, present on admission; sCP, standard chemoprophylaxis; VTE, venous thromboembolism.

Patients that received sCP+A were older, had a higher rate of obesity, were more severely injured, had a longer length of stay, and more ventilator days. In addition, they had a higher TESS. There were no differences in the incidences of elevated thromboelastography (TEG) maximum amplitude (MA) levels. Patients that received sCP+A had higher rates of preadmission antiplatelet and vitamin K antagonist use (table 1).

Patients that received sCP+A had more known risk factors for VTE.[2 28] Patients who received sCP+A were more likely to have had operations lasting longer than 2 hours, central venous lines, venous injuries requiring repair, blood transfusions of greater than four units, spine fractures, spinal cord injuries, cardiovascular disease, smoking history, or chronic obstructive pulmonary disease (COPD) (table 1).

Time to prophylaxis regimen

The median time to initiation of sCP was 1.39 (0.86, 2.3) days, which was statistically shorter than the sCP+A cohort (1.4 (0.87, 2.42) days, p<0.01). The majority (75.4%) of patients received LMWH as their primary chemoprophylaxis regimen, which was similar between the two studied groups (sCP 75.6% vs sCP+A 74.5%, p=0.32).

The median time from admission to initiation of aspirin in the 1886 patients within the sCP+A cohort was 3 (1, 6) days. The reasons for starting aspirin were due to a myocardial infarction (n=22, 1.2%), a stroke (n=9, 0.5%), blunt cerebrovascular injury (n=332, 17.6%), either a history of cardiovascular disease or known pre-admission aspirin use (n=947, 50.2%), or at the discretion of the rounding physician (n=576, 30.5%). Of the patients receiving aspirin, 47.4% received 325 mg, 47.7% received 81 mg, and 5.1% received an alternate dose of aspirin.

Primary outcome

Three hundred fifty-three patients were diagnosed with a new, symptomatic VTE during their hospitalization (sCP 2.81% vs sCP+A 5.83%, p<0.01) (figure 1). The median day patients on sCP were diagnosed with a VTE was hospital day 5 (2, 5) compared with sCP+A on hospital day 6 (4, 6) (p=0.03).

Using a Cox proportional hazard model, after adjusting for the dose of UFH or LMWH, major venous repair, and TESS, receiving aspirin of any dose was associated with a decreased risk of VTE (HR 0.57, 95% CI 0.36 to 0.88, p=0.01) (table 2). The absolute risk reduction was 1.8% with a number needed to treat of 55 at 60 days.

However, the dosage of aspirin that contributed to a decreased risk of VTE could not be elucidated based on this analysis (81 mg (HR 0.84, 95% CI 0.62 to 1.1, p=0.23); 325 mg (HR 0.85, 95% CI 0.59 to 1.2, p=0.37)). In addition, despite identifying an association between aspirin and a decreased risk of overall VTE and DVT (HR 0.57, 95% CI 0.36 to 0.88, p=0.01), a decreased risk of PE (HR 0.78, 95% CI 0.58 to 1.1, p=0.08) was not able to be established.

Secondary outcomes

Bleeding complications

After adjusting for blood transfusion of at least four units, central venous line, prolonged operation (greater than 2 hours)

Table 1 Demographic, injury, and VTE risk factors by chemoprophylaxis regimen

	sCP	sCP+A	Total	P value
	(n=8646)	(n=1886)	(n=10,532)	(sCP vs sCP+A)
Age (years)*	42 (27, 59)	56 (35, 72)	44 (28, 62)	<0.001
Sex (% male)	5879 (68)	1264 (67)	7143 (68)	0.21
Mechanism (% blunt)	7695 (89)	1697 (90)	9392 (89)	0.17
Admission GCS score	15 (14, 15)	15 (14, 15)	15 (14, 15)	0.18
Morbid obesity (%)*	2009 (23)	491 (26)	2500 (24)	0.03
ISS*	11 (9, 18)	13 (9, 21)	12 (9, 19)	<0.001
Lower extremity fracture (%)*	2013 (23)	472 (25)	2485 (24)	0.10
Length of stay (days)	5 (3, 10)	10 (5, 18)	6 (3, 11)	<0.001
Ventilator (days)	0 (0, 0)	0 (0, 1)	0 (0, 0)	<0.001
Prolonged ventilation (%)*	865 (10)	296 (16)	1161 (11)	<0.001
TESS	4 (2, 5)	4 (2, 6)	4 (2, 5)	<0.001
Admission TEG maximum amplitude	64 (59, 68)	64 (59, 68)	64 (59, 68)	0.81
Admission TEG maximum amplitude >65 (%)	3692 (43)	868 (46)	4560 (43)	0.11
Admission TEG maximum amplitude >72 (%)	830 (10)	202 (11)	1010 (10)	0.42
Preadmission anticoagulant or antiplatelet therapy (%)	338 (4)	217 (12)	555 (5)	< 0.001
Heparinoid (any dose) (%)	0.1	0.3	0.1	0.09
Antiplatelet (%)	2	7.2	2.9	< 0.001
Vitamin K antagonist (%)	1.4	3.2	1.7	< 0.001
Direct Xa inhibitor (%)	0.2	0.3	0.2	0.25
Direct thrombin inhibitor (%)	0.2	0.2	0.2	0.89
Other risk factors (%)				
Operation >2 hours	3248 (38)	971 (52)	4219 (40)	< 0.001
Central venous line	799 (9)	744 (22)	1210 (12)	<0.001
Major venous injury/repair	222 (3)	123 (7)	345 (3)	<0.001
Blood products, >4 units	614 (7)	212 (11)	826 (8)	< 0.001
IVC filter placement	222 (3)	123 (7)	345 (3)	< 0.001
Spine fracture	2326 (27)	597 (32)	2923 (28)	< 0.001
Spinal cord injury	136 (2)	43 (2)	179 (2)	0.03
Pelvis fracture	1150 (13)	250 (13)	1400 (13)	0.88
Cardiovascular disease	2561 (30)	935 (50)	3496 (33)	< 0.001
COPD	193 (2)	87 (5)	280 (3)	< 0.001
Smoker	1989 (23)	343 (18)	2332 (22)	< 0.001
Malignancy (active or history of)	53 (0.6)	14 (0.7)	67 (0.6)	0.52

Risk factors for VTE in patients with standard chemoprophylaxis compared with patients with adjunctive aspirin. All values are reported as raw numbers with percentages as indicated or median values with associated interquartile ranges.
Morbid obesity defined as body mass index of greater than 35 kg/m^2.
Heparinoid includes unfractionated heparin or low molecular weight heparin.
*Included in TESS.
COPD, Chronic Obstructive Pulmonary Disease; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; IVC, Inferior Vena Cava; sCP, standard chemoprophylaxis; TEG, thromboelastography; TESS, Trauma Embolic Scoring System. A TESS of 6 or higher is predictive of a higher risk of VTE; VTE, venous thromboembolism.

Table 2 Cox proportional hazard model—risk of VTE

	HR	95% CI	P value
Major venous repair	2.81	1.78 to 4.45	<0.01
Central venous catheter	2.38	1.59 to 3.56	<0.01
Trauma Embolic Scoring System	1.09	1.03 to 1.15	0.01
Subprophylactic enoxaparin*	1.08	0.70 to 1.67	0.73
Subprophylactic heparin*	6.09	3.29 to 11.27	<0.01
Aspirin (any dose)	0.57	0.36 to 0.88	0.01

*Doses of anticoagulation given at levels under the institutional guidelines and/or missed doses with adequate prophylactic dosing representing the reference category for comparison.

Table 3 Bleeding complications

	Point estimate	95% CI	P value
Blood transfusion, >4 units	7.78	4.45 to 13.61	<0.001
Central venous catheter	19.45	5.27 to 71.8	<0.001
Central venous catheter, femoral	0.27	0.08 to 0.92	0.04
Prolonged operation, >2 hours	2.35	1.16 to 4.77	0.02
sCP	2.31	1.27 to 4.21	0.01
Cardiovascular disease	0.38	0.18 to 0.79	0.01
Aspirin (any dose)	1.23	0.68 to 2.21	0.50

sCP, standard chemoprophylaxis.

and cardiovascular disease, there were no differences in bleeding complications in patients that received sCP compared with sCP+A (point estimate 1.23, 95%CI 0.68 to 2.2, p=0.50) (table 3).

DISCUSSION

Despite targeted efforts to reduce the incidence of VTE after traumatic injury through risk stratification, improved and earlier chemoprophylaxis dosing, and the use of various mechanical mitigation strategies, the rate of VTE within trauma populations remains high among severely injured patients and VTE prevention is regarded one of the top priorities toward improving patient safety.[2 29 30] In the current study, we demonstrated that adjunctive use of aspirin with standard chemoprophylaxis was independently associated with a 43% reduction in the hazard rate of developing VTE in trauma patients without an increased risk of associated bleeding complications. Moreover, this reduction in VTE was observed despite sCP+A patients having a greater number of risk factors and higher calculated baseline risk for VTE, compared with sCP only patients. These findings support our hypothesis that antiplatelet therapy may have a role as an adjunct to standard chemoprophylaxis regimens for decreasing the risk of developing VTE after traumatic injury.

Antiplatelet therapy has long been implicated in the risk reduction of arterial thrombosis (myocardial infarction, stroke, acute limb ischemia, etc); however, its role in the prevention of venous thrombosis, particularly following non-orthopedic trauma, has not been fully examined.[31 32] The Antiplatelet Trialist's Collaboration meta-analysis of over 50 trials in medical and surgical patients demonstrated a 10% decreased rate of DVT and a 64% relative risk reduction in PE with the use of antiplatelet therapy for 2 weeks postoperatively.[31 33] The Pulmonary Embolism Prevention (PEP) trial, a multicenter, randomized controlled trial conducted in over 13,000 orthopedic surgical patients, also demonstrated that perioperative aspirin resulted in a 43% reduction in PE and 23% reduction in DVT when used in combination with additional chemoprophylaxis at the discretion of the operating surgeon.[20] Aspirin alone was subsequently found to be non-inferior to LMWH for VTE prevention in patients after unilateral total hip arthroplasty over their standard course of postoperative monitoring (1.3% vs 0.3%, p=0.22).[19] As a result of these studies, the American College of Chest Physicians, American Academy of Orthopedic Surgeons, and European Society of Anesthesiology have stated that aspirin is an acceptable component of multimodal VTE prophylaxis for patients undergoing major elective orthopedic operation.[34–36]

Trauma patients, however, represent a unique patient population with the potential to display altered platelet function based on viscoelastic testing. Previous studies have demonstrated that patients within this population who display elevated TEG MA and G values, markers for increased platelet activity and fibrin activity, are at increased risk for VTE despite appropriate VTE prophylaxis.[10 37–39] Taken together, these data suggest a unimodal approach to VTE chemoprophylaxis focusing solely on the thrombin-based component of clot formation may be insufficient.[10 11] Despite this, there remains a paucity of literature assessing the effects of antiplatelet medication on VTE formation in trauma patients.

Brill *et al* assessed the relationship between preinjury aspirin use with DVT formation and concluded that preinjury aspirin use in trauma patients was associated with a lower odds of in hospital DVT formation for those receiving heparinoid chemoprophylaxis (OR 0.35, 95%CI 0.13 to 0.93).[12] The proposed protective effect of preinjury aspirin use displayed by Brill *et al* is in agreement with our findings suggesting antiplatelet medication may safely help to decrease VTE risk.

Of particular interest, Haac *et al* assessed aspirin versus LMWH as the sole VTE chemoprophylaxis regimen in orthopedic trauma patients and found no evidence of superiority on Global Rank test for either regimen.[23] The Major Extremity Trauma Research Consortium subsequently followed with their multicenter, randomized control trial (PREVENT CLOT trial) which similarly found aspirin to be safe and non-inferior to LMWH with regard to mortality.[24] Despite these studies being the first randomized trials to compare aspirin as a sole agent with LMWH for VTE mitigation, their focus on isolated orthopedic trauma patients yields findings that cannot be directly translated to the critically ill polytrauma patient, especially those that survive hemorrhagic shock.

Although no studies currently exist comparing standard regimens with aspirin monotherapy in polytrauma patients, the findings of our study, which suggest an additive benefit of adjunctive aspirin to standard chemoprophylaxis regimens for VTE reduction, support the need for ongoing prospective evaluation of the antiplatelet medications for VTE chemoprophylaxis in the broader trauma populations. Moreover, many authors have previously shown that VTE is most common within the first week of injury with continuation of subsequent risk for many weeks after discharge.[3 20 40–42] Although our data suggest the benefits of early aspirin use in the polytrauma population, prospective study assessing continued aspirin administration following discharge should be assessed. If effective, the potential for decreased cost and ease of use associated with aspirin compared with LMWH may make it an attractive possibility.

Our current study does have several limitations. This analysis represents the largest evaluation of aspirin for VTE mitigation in non-orthopedic trauma patients; however, the retrospective nature of this study creates findings that can only be viewed as hypothesis generating, are at risk for the potential of type II error, and are inherently dependent on the reliability of the databases assessed. A subset of the patients from this study were on aspirin prior to arrival as a home medication and it remains plausible that the antiplatelet effects present at the time of injury may have played a role in VTE mitigation as opposed to post-injury aspirin initiation. Thus, future prospective analyses will be required to fully analyze the reported association.

Individual injury patterns were not directly assessed due to the granularity of the queried datasets. Further, traumatic brain injury (TBI) patients were included within our population and may represent a confounding factor due to the inherently different coagulation profiles associated with TBI patients. As patients were not randomized to distinct groups, aspirin administration was by in large left to the discretion of the attending physician, generating a selection bias, although toward sicker patients. Routine screening for VTE was not conducted during this study therefore the generalizability of our results to the rate of VTE in an institution that does screen for VTE may be misrepresented. Our findings, which reveal a lower rate of VTE compared with prior studies, further highlight that asymptomatic VTE in patients may not have been captured due to the lack of routine screening. That said, routine screening for VTE in trauma patients is not ubiquitous and, thus, our findings remain relevant for the multitude of trauma centers that do not routinely screen for VTE. Although the relationship between interruptions in chemoprophylaxis and the rate of DVT has been documented, we did not include this in our model due to inherent limitations within the dataset.[43] Nevertheless, the institutional guidelines for

VTE prophylaxis in this study included early administration of chemoprophylaxis immediately after admission in the absence of a contraindication or within 24 hours after cessation of bleeding. A subset of patients within this study, however, received heparin as their primary chemoprophylaxis. Although this strategy was used based on their associated clinical findings that restricted use of LMWH based on institutional policy, heparin is thought to be an inferior agent to LMWH with regard to VTE prophylaxis in trauma and may result in an altered risk factor profile compared with those who received LMWH. Beyond this, chemoprophylactic dosing adjustments based on clinical findings were not captured during this analysis, resulting in an inability to adjust for dosing changes within the statistical models. In addition, the use of thromboembolic deterrent hose and sequential compression devices in the absence of a wound that precludes their placement are routinely employed; however, compliance with these practices was not collected in these databases and was not verified through chart review. Although early walking may help decrease VTE occurrence, time to walking was unable to be captured within our dataset and therefore was also not assessed. The administration of tranexamic acid, which has been widely debated regarding its potential thrombogenicity, was also not evaluated within this study. Although 47% of patients were on 325 mg of aspirin, we could not elucidate a difference in the dosage of aspirin (81 mg vs 325 mg) that contributed to the reduced risk of VTE. Thus, optimal dosing strategies still need to be elucidated. Beyond identifying the optimal dosing regimen, it remains possible that only select patient cohorts may benefit from the addition of aspirin. We speculate that patients who display increased platelet activity via TEG-based analysis may derive the greatest potential benefit from aspirin administration. This concept, however, has yet to be formally evaluated. Finally, aspirin resistance was not assessed within this study.[44]

CONCLUSION

In this current study of over 10,000 trauma patients, we demonstrated that the addition of aspirin to standard VTE chemoprophylaxis regimens was associated with a 43% reduction in the hazard rate of developing a VTE after injury without an increase in bleeding complications. Further prospective analysis should be sought to effectively identify optimal patient populations and VTE chemoprophylaxis strategies prior to routine incorporation in clinical practice.

Contributors MS, AD, JT, CCM, and JBH developed the idea for this study. DL, MS, and MP conducted the literature search. DL, MS, AD, MP, CEW, JC, JJ, CCM, and JBH contributed to study design. MS, AD, MP, JT, and JBH participated in data acquisition. DL, MS, CEW, JC, CCM, JJ, and JBH contributed to the data analysis and interpretation. DL, MS drafted the article. AD, MP, JT, CEW, JC, JJ, CCM, and JBH critically revised the final article. All authors reviewed and approved the final article. JBH is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be made available on reasonable request.

ORCID iDs
Daniel Lammers http://orcid.org/0000-0002-9489-3633
Jan Jansen http://orcid.org/0000-0001-8863-4398

REFERENCES

1 Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev* 2013:CD008303.
2 Knudson MM, Gomez D, Haas B, Cohen MJ, Nathens AB. Three thousand seven hundred thirty-eight Posttraumatic pulmonary emboli: a new look at an old disease. *Ann Surg* 2011;254:625–32.
3 Menaker J, Stein DM, Scalea TM. Incidence of early pulmonary embolism after injury. *J Trauma Acute Care Surg* 2007;63:620–4.
4 Gunning AC, Maier RV, de Rooij D, Leenen LPH, Hietbrink F. Venous thromboembolism (VTE) prophylaxis in severely injured patients: an international comparative assessment. *Eur J Trauma Emerg Surg* 2021;47:137–43.
5 Regner JL, Shaver CN, Frazee R, Brooks SE, Dissanaike S, Brown CV, Pieracci FM, Burlew CC, Davis JW, Dirks R. Determining the impact of culture on venous thromboembolism prevention in trauma patients: a Southwestern surgical congress multicenter trial. *Am J Surg* 2019;217:1030–6.
6 Frith D, Davenport R, Brohi K. Acute traumatic coagulopathy. *Curr Opin Anaesthesiol* 2012;25:229–34.
7 Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ. Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma* 2005;58:475–80.
8 Harrigan C, Lucas CE, Ledgerwood AM. The effect of hemorrhagic shock on the clotting cascade in injured patients. *J Trauma* 1989;29:1416–21;
9 Sumislawski JJ, Kornblith LZ, Conroy AS, Callcut RA, Cohen MJ. Dynamic coagulability after injury: is delaying venous thromboembolism chemoprophylaxis worth the wait *J Trauma Acute Care Surg* 2018;85:907–14.
10 Cotton BA, Minei KM, Radwan ZA, Matijevic N, Pivalizza E, Podbielski J, Wade CE, Kozar RA, Holcomb JB. Admission rapid thrombelastography predicts development of pulmonary embolism in trauma patients. *J Trauma Acute Care Surg* 2012;72:1470–5;
11 Harr JN, Moore EE, Chin TL, Ghasabyan A, Gonzalez E, Wohlauer MV, Banerjee A, Silliman CC, Sauaia A. Platelets are dominant contributors to hypercoagulability after injury. *J Trauma Acute Care Surg* 2013;74:756–62.
12 Brill JB, Calvo RY, Wallace JD, Lewis PR, Bansal V, Sise MJ, Shackford SR. Aspirin as added prophylaxis for deep vein thrombosis in trauma: a retrospective case-control study. *J Trauma Acute Care Surg* 2016;80:625–30.
13 Matthay ZA, Hellmann ZJ, Nunez-Garcia B, Fields AT, Cuschieri J, Neal MD, Berger JS, Luttrell-Williams E, Knudson MM, Cohen MJ, *et al*. Post-injury platelet aggregation and venous thromboembolism. *J Trauma Acute Care Surg* 2022;93:604–12.
14 Karcutskie CA, Dharmaraja A, Patel J, Eidelson SA, Padiadpu AB, Martin AG, Lama G, Lineen EB, Namias N, Schulman CI, *et al*. Association of anti–factor Xa–guided dosing of enoxaparin with venous thromboembolism after trauma. *JAMA Surg* 2018;153:144–9.
15 Verhoeff K, Raffael K, Connell M, Kung JY, Strickland M, Parker A, Anantha RV. Relationship between anti-Xa level achieved with prophylactic low-molecular weight heparin and venous thromboembolism in trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg* 2022;93:e61–70.
16 Rakhra S, Martin E-L, Fitzgerald M, Udy A. The ATLANTIC study: anti-Xa level assessment in trauma intensive care. *Injury* 2020;51:10–4.
17 Knudson MM, Moore EE, Kornblith LZ, Shui AM, Brakenridge S, Bruns BR, Cipolle MD, Costantini TW, Crookes BA, Haut ER, *et al*. Challenging traditional paradigms in posttraumatic pulmonary thromboembolism. *JAMA Surg* 2022;157:e216356.
18 Brakenridge SC, Henley SS, Kashner TM, Golden RM, Paik D-H, Phelan HA, Cohen MJ, Sperry JL, Moore EE, Minei JP, *et al*. Comparing clinical predictors of deep venous thrombosis vs. pulmonary embolus after severe injury: a new paradigm for post-traumatic venous thromboembolism *J Trauma Acute Care Surg* 2013;74:1231–7;
19 Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, Fisher W, Gofton W, Gross P, Pelet S, *et al*. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med* 2013;158:800.
20 O'Brien J, Duncan H, Kirsh G, Allen V, King P, Hargraves R. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. *The Lancet* 2000;355:1295–302.
21 Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, *et al*. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012;367:1979–87.
22 Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, *et al*. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012;366:1959–67.
23 Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, Stein DM, ADAPT Investigators. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: a patient-centered randomized controlled trial. *PLoS One* 2020;15:e0235628.
24 Major Extremity Trauma Research Consortium (METRC), O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, Carlini AR, Sudini K, Degani Y, *et al*. Aspirin or

low-molecular-weight heparin for thromboprophylaxis after a fracture. *N Engl J Med* 2023;388:203–13.
25 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
26 Rogers FB, Shackford SR, Horst MA, Miller JA, Wu D, Bradburn E, Rogers A, Krasne M. Determining venous thromboembolic risk assessment for patients with trauma: the trauma embolic scoring system. *J Trauma Acute Care Surg* 2012;73:511–5.
27 Ho KM, Rao S, Rittenhouse KJ, Rogers FB. Use of the trauma embolic scoring system (TESS) to predict symptomatic deep vein thrombosis and fatal and non-fatal pulmonary embolism in severely injured patients. *Anaesth Intensive Care* 2014;42:709–14.
28 Gearhart MM, Luchette FA, Proctor MC, Lutomski DM, Witsken C, James L, Davis K Jr, Johannigman JA, Hurst JM, Frame SB. The risk assessment profile score identifies trauma patients at risk for deep vein thrombosis. *Surgery* 2000;128:631–40.
29 Henke PK, Kahn SR, Pannucci CJ, Secemksy EA, Evans NS, Khorana AA, Creager MA, Pradhan AD, American Heart Association Advocacy Coordinating Committee. Call to action to prevent venous thromboembolism in hospitalized patients: a policy statement from the American Heart Association. *Circulation* 2020;141:e914–31.
30 Shekelle PG, Pronovost PJ, Wachter RM, McDonald KM, Schoelles K, Dy SM, Shojania K, Reston JT, Adams AS, Angood PB, *et al*. The top patient safety strategies that can be encouraged for adoption now. *Ann Intern Med* 2013;158:365–8.
31 Collaboration AT. Antithrombotic trialists' collaboration. collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
32 Undas A, Brummel-Ziedins KE, Mann KG. Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. *Blood* 2007;109:2285–92.
33 Cohen AT, Skinner JA, Kakkar VV. Antiplatelet treatment for thromboprophylaxis: a step forward or backwards? *BMJ* 1994;309:1213–5.
34 Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012;141:7S–47S.
35 Stewart DW, Freshour JE. Aspirin for the prophylaxis of venous thromboembolic events in orthopedic surgery patients: a comparison of the AAOS and ACCP guidelines with review of the evidence. *Ann Pharmacother* 2013;47:63–74.
36 Jenny J-Y, Pabinger I, Samama CM, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: aspirin. *Eur J Anaesthesiol* 2018;35:123–9.
37 McCrath DJ, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. *Anesth Analg* 2005;100:1576–83.
38 Wilson D, Cooke EA, McNally MA, Wilson HK, Yeates A, Mollan RA. Changes in coagulability as measured by thrombelastography following surgery for proximal femoral fracture. *Injury* 2001;32:765–70.
39 Kashuk JL, Moore EE, Sabel A, Barnett C, Haenel J, Le T, Pezold M, Lawrence J, Biffl WL, Cothren CC, *et al*. Rapid Thrombelastography (R-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery* 2009;146:764–74.
40 Harr JN, Moore EE, Chin TL, Ghasabyan A, Gonzalez E, Wohlauer MV, Banerjee A, Silliman CC, Sauaia A. Platelets are dominant contributors to hypercoagulability after injury. *J Trauma Acute Care Surg* 2013;74:756–65.
41 Owings JT, Kraut E, Battistella F, Cornelius JT, O'Malley R. Timing of the occurrence of pulmonary embolism in trauma patients. *Arch Surg* 1997;132:862–6.
42 Coleman JJ, Zarzaur BL, Katona CW, Plummer ZJ, Johnson LS, Fecher A, O'Rear JM, Feliciano DV, Rozycki GS. Factors associated with pulmonary embolism within 72 hours of admission after trauma: a multicenter study. *J Am Coll Surg* 2015;220:731–6.
43 Louis SG, Sato M, Geraci T, Anderson R, Cho SD, Van PY, Barton JS, Riha GM, Underwood S, Differding J, *et al*. Correlation of missed doses of enoxaparin with increased incidence of deep vein thrombosis in trauma and general surgery patients. *JAMA Surg* 2014;149:365–70.
44 Ebrahimi P, Farhadi Z, Behzadifar M, Shabaninejad H, Gorji HA, Mirghaed MT, *et al*. Prevalence rate of laboratory defined aspirin resistance in cardiovascular disease patients: a systematic review and meta-analysis. *Casp J Intern Med* 2020;11:124.