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Thromboprophylaxis in hospitalized trauma patients: a systematic review and meta-analysis of implementation strategies

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ABSTRACT

Introduction Venous thromboembolism (VTE) prophylaxis implementation strategies are well-studied in some hospitalized medical and surgical patients. Although VTE is associated with substantial mortality and morbidity in trauma patients, implementation strategies for the prevention of VTE in trauma appear to be based on limited evidence. Therefore, we conducted a systematic review and meta-analysis of published literature on active implementation strategies for VTE prophylaxis administration in hospitalized trauma patients and the impact on VTE events.

Methods A systematic review and meta-analysis was performed in adult hospitalized trauma patients to assess if active VTE prevention implementation strategies change the proportion of patients who received VTE prophylaxis, VTE events, and adverse effects such as bleeding or heparin-induced thrombocytopenia as well as hospital length of stay and the cost of care. An academic medical librarian searched Medline, Scopus, and Web of Science until December 2022.

Results Four studies with a total of 1723 patients in the active implementation strategy group (strategies included education, reminders, human and computer alerts, audit and feedback, preprinted orders, and/or root cause analysis) and 1324 in the no active implementation strategy group (guideline creation and dissemination) were included in the analysis. A higher proportion of patients received VTE prophylaxis with an active implementation strategy (OR=2.94, 95% CI (1.68 to 5.15), p<0.01). No significant difference was found in VTE events. Quality was deemed to be low due to bias and inconsistency of studies.

Conclusions Active implementation strategies appeared to improve the proportion of major trauma patients who received VTE prophylaxis. Further implementation studies are needed in trauma to determine effective, sustainable strategies for VTE prevention and to assess secondary outcomes such as bleeding and costs.

Level of evidence Systematic review/meta-analysis, level III.

PROSPERO registration number CRD42023390538.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies regarding venous thromboembolism (VTE) prophylaxis administration and guideline implementation exist in hospitalized medical and surgical patients, however are scarce in the trauma population.

WHAT THIS STUDY ADDS

⇒ This systematic review demonstrated that active implementation strategies increased the proportion of patients who received VTE prophylaxis; however, there is a scarcity of VTE prophylaxis implementation science research in trauma patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further implementation science research is required to assess VTE prophylaxis prescribing patterns, its effects on VTE events, bleeding events, and costs of care.

INTRODUCTION

Venous thromboembolism (VTE) is an important cause of morbidity and mortality in hospitalized trauma patients. The incidence of VTE in major trauma patients is as high as 58% without prophylaxis.[1 2] Pulmonary embolism (PE) is the third leading cause of preventable mortality in hospitals and the number one cause of preventable mortality in trauma after the first 24 hours.[3] Many clinical practice guidelines (CPGs) have established that early, uninterrupted VTE prophylaxis is effective and safe.[4–9] Despite prophylaxis measures becoming more commonplace, VTE prophylaxis continues to be underutilized.[10] Previous systematic reviews of hospitalized surgical and medical patients have suggested that multifaceted approaches to VTE prophylaxis prescribing have been the most effective.[11 12] These approaches have involved active strategies and computer-based alerts which were shown to improve prescribing more than passive strategies, such as dissemination of a guideline. Active strategies that have been commonly utilized and studied include human alerts with team ward rounds and pharmacist reviews; electronic alerts; pre-printed orders or computerized provider order entry (CPOE); audit and feedback; and root cause analysis of suboptimal thromboprophylaxis and/or clinical events. Although most of these studies have been focused on hospitalized medical and surgical patients, studies in trauma have been scarce.

The rationale for this study is to review system-wide interventions to increase the utilization of venous thromboprophylaxis and decrease the incidence of VTE in hospitalized trauma patients.

OBJECTIVE

The primary objective was to assess the effects of active VTE prevention implementation strategies compared with passive strategies on adherence to thromboprophylaxis use and on VTE rates in adult hospitalized trauma patients. Secondary objectives were to assess the impact of active VTE prevention implementation strategies on adverse effects of thromboprophylaxis, length of stay (LOS), and costs of care.

Population, Intervention, Comparison, and Outcome

The following Population, Intervention, Comparison, and Outcome (PICO) stem was formulated prior to a literature search: in adult hospitalized trauma patients aged ≥15 years, what are the effects of active VTE prevention implementation strategies on the proportion of patients who received VTE prophylaxis, development of VTE, and adverse effects such as bleeding or heparin-induced thrombocytopenia, as well as on the hospital LOS and on the costs of care? LOS was defined from admission to discharge home, to a rehabilitation center or reactivation unit, transfer to another acute care facility, or death in hospital.

Active VTE implementation strategies assessed one or more of the following:

1. Human alerts—team ward rounds, pharmacist reviews
2. Electronic alerts
3. Pre-printed orders or CPOE
4. Audit and feedback
5. Root cause analysis of suboptimal thromboprophylaxis and/or clinical events

Passive strategies are guideline creation and dissemination. The outcomes that were assessed included the following:

a. Proportion of patients who received VTE prophylaxis.
b. Proportion of patients who received appropriate VTE prophylaxis. Appropriate VTE prophylaxis was defined by each respective study as abided by their own institutional protocols.
c. Proportion of patients who developed VTE
d. Proportion of patients who developed VTE prophylaxis-related bleeding complications or heparin-induced thrombocytopenia (HIT)
e. Proportion of patients who received a prophylactic inferior vena cava (IVC) filter.
f. LOS
g. Cost of care

METHODS

A systematic review and meta-analysis was performed. This study was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (PRISMA checklist, online supplemental table 1).[13] A protocol outlining the methods of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023390538). The search strategy was developed and executed in December 2022 in consultation with an experienced medical librarian from Medical College of Wisconsin Libraries (EH) from inception to December 12, 2022. The search strategy was created for Ovid MEDLINE using a combination of Medical Subject Heading (MeSH) terms, keywords, and phrases (search strategy available in online supplemental table 2). Search terms targeted VTE prophylaxis, guidelines, and protocols—all in a trauma setting. The strategy was translated to other databases, including Scopus and Web of Science, using their respective thesaurus terms and advanced search features. Inclusion criteria included: studies in the English language, randomized, retrospective, or observational studies, reported on a thromboprophylaxis implementation intervention and had a comparison group, and reported on the outcomes of interest. Case series and commentaries were excluded. Reviews were assessed to ensure their referenced primary studies were included in our results. Titles, abstracts, and full texts were reviewed in duplicate independently by two authors (AR, SS, MC, KP, AG), and any disagreements were adjudicated by the primary author (AR). All reviews took place using Rayyan (https://www.rayyan.ai/). Data were also extracted in duplicate in Excel (Microsoft, Redmond, WA) and meta-analyzed on RevMan Online (revman.cochrane.org). The certainty of the evidence was assessed with GRADEPro (www.gradepro.org) taking into consideration potential risks of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, and the effect of plausible residual confounders on demonstrated effect. The Mantel-Haenszel method with random effects modeling was used to calculate pooled ORs (95% CIs) for outcomes. Statistical significance was set at $p<0.05$. Heterogeneity was calculated and quantified with I^2. Low degree of heterogeneity had I^2 values less than 50%; those with moderate heterogeneity had I^2 values of 50% to 74%; I^2 values >75% were indicative of high heterogeneity.[14]

RESULTS

The literature search initially yielded 7764 studies, of which 4 met criteria for inclusion and were analyzed (figure 1).

The PICO question was in adult hospitalized trauma patients aged ≥16 years, does active VTE prophylaxis implementation strategies compared with passive implementation strategies increase the proportion of patients who received VTE prophylaxis, decrease VTE and adverse events such as bleeding or heparin-induced thrombocytopenia as well as hospital LOS and cost of care? A VTE event was defined as the development of deep venous thrombosis (DVT) or PE, either symptomatic, found incidentally on imaging obtained for other reasons or on screening Doppler ultrasound. The included studies and their characteristics are summarized in table 1 and excluded studies and reasons for exclusion are summarized in online supplemental table 3.

Qualitative analysis

None of the studies were randomized trials. Studies by Haut *et al*,[15] Engels *et al*,[16] and Tignanelli *et al*[17] were retrospective, whereas the study by Burns *et al*[18] had both retrospective and prospective components. Burns *et al* studied 134 acute spinal cord injury patients in six VA hospitals in the United States.[18] The authors measured adherence to the 1997 Consortium for Spinal Cord Medicine VTE CPG after targeted implementation strategies based on standardized orders, nursing flow sheet documentation, and provider education. Reviews were performed across three time periods: before and after publication of the CPG and after implementation strategies. Publication of the CPG alone had no significant effect on the use of pharmacologic thromboprophylaxis (38% vs. 43%), while active implementation strategies increased adherence to the CPG and, therefore, increased the administration of thromboprophylaxis (from 38% to 60%). Haut *et al*[15] performed

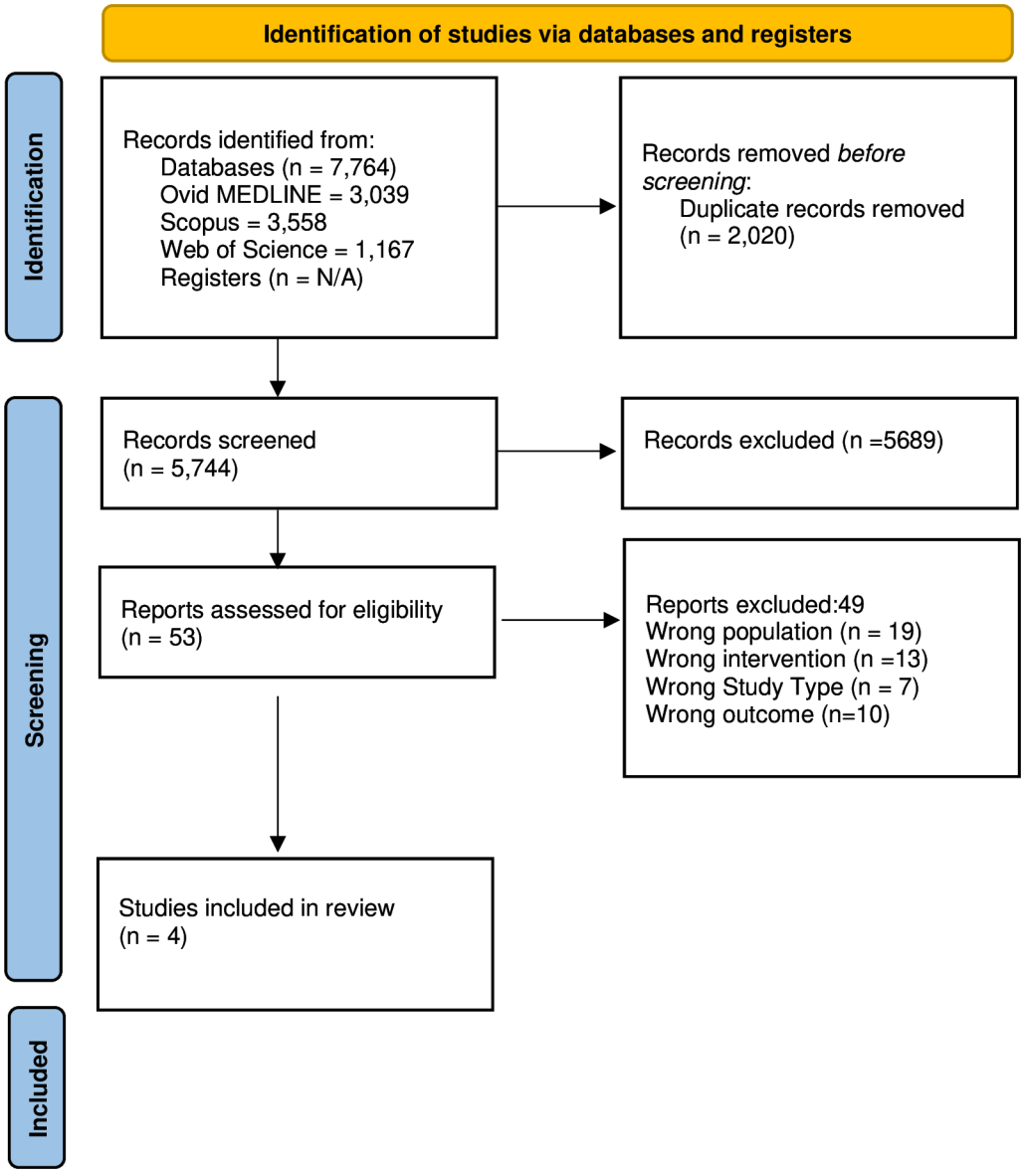

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis of included studies.

a retrospective study in 1599 patients at a level 1 trauma center in which the intervention was the implementation of a mandatory computerized provider entry-based clinical decision support tool. Compliance with the local VTE prophylaxis guideline was increased from 66% to 84%, and there was a decrease in potentially preventable VTE events (from 1.0% to 0.2%). Engels *et al* [16]performed a retrospective study on 633 patients at a level 1 trauma center to see if consultations with the thrombosis service improved VTE prophylaxis administration. The authors demonstrated an increase in VTE prophylaxis administration (from 79% to 88%) when the thrombosis service was consulted; however, no differences were observed in VTE events. Tignanelli and colleagues[17] performed a retrospective study in 681 traumatic brain injury patients before and after implementing a new protocol for thromboprophylaxis and by incorporating thromboprophylaxis into daily nursing notes, education and weekly audits and feedback. The authors demonstrated an increase in anticoagulant VTE prophylaxis administration (39% vs. 81%) and a reduction in VTE events (5.2% vs. 2.2%).

Quantitative analysis

Proportion of patients who received VTE prophylaxis

In the pooled analysis of all four studies, there were a total of 1324 patients in the active implementation strategy group and 1723 patients in the no active implementation strategy group. The analysis demonstrated a significant increase in the proportion of patients who received prophylaxis after an active implementation strategy (from 62.8% to 83.7%; OR=2.94, 95% CI (1.68 to 5.15), p=0.0002) (figure 2).

VTE events

All included studies reported the number of VTE events. There were 51 VTE events out of 1324 patients (3.9%) in the no active implementation strategy group and 43 VTE events in 1723 patients (2.5%) in the active implementation strategy group. In the pooled analysis, no significant difference was found between the two groups (OR=0.86, 95% CI (0.43 to 1.71), p=0.66) (figure 3).

Other outcomes

None of the included studies reported on bleeding complications, incidence of HIT, prophylactic IVC filter use, or

Table 1 Description of all included studies

Study	Study type	Patient population	Active interventions	Comparison	Intervention (N)	Comparison (N)	Results	Study conclusion
Burns *et al*[18]	Retrospective and prospective review	Acute SCI; 6 Veteran Affairs SCI Centers	1. Pre-printed orders or CPOE: standing orders/ standardized documentation templates 2. Audit and feedback: medical record review 3. Education events: social marketing/outreach visit	No CPG initiation	46	88	Use of the specified duration for pharmacologic prophylaxis increased from 60% to 65% to 75% of patients with acute SCI in period before guideline publication (T1), after guideline publication (T2), and after dissemination and implementation (T3), respectively (p=0.060 and 0.041 for T1 vs. T2 and T2 vs. T3, respectively). DVT was diagnosed in 7.8%, 7.9%, and 17.9% of patients with acute SCI during T1, T2, and T3, respectively (p=0.70 and 0.33 for T1 vs. T2 and T2 vs. T3, respectively)	The CPG publication had only a modest effect on practice. Use of structured implementation further increased the adherence to some CPG recommendations for thromboembolism prophylaxis
Haut *et al*[15]	Retrospective review	Adult trauma patients hospitalized for >1 day; single institution	Pre-printed orders or CPOE: mandatory CDS module	No CDS module	1200	399	Compliance with guideline-appropriate prophylaxis increased from 66.2% to 84.4% (p=0.001). The rate of preventable harm from VTE decreased from 1.0% to 0.17% (p=0.04).	Implementation of a mandatory computerized provider order entry–based clinical decision support tool significantly improved compliance with VTE prophylaxis guidelines in hospitalized adult trauma patients. This improved compliance was associated with a significant decrease in the rate of preventable harm.
Engels *et al*[16]	Retrospective review	Trauma patients, age >16 years hospitalized for >1 day; single institution	Human alerts: thrombosis service consultation	Without thrombosis service consultation	164	469	Patients seen by the thrombosis service were more likely to receive VTE prophylaxis than those not seen by the service (145 (88.4%) vs. 369 (78.7%), p<0.01)	Thrombosis consultation service improved compliance with VTE prophylaxis

Continued

Table 1 Continued

Study	Study type	Patient population	Active interventions	Comparison	Intervention (N)	Comparison (N)	Results	Study conclusion
Tignanelli *et al*[17]	Retrospective review	All TBI patients (AIS≥2); single institution	1. Human alerts: daily ICU/floor rounds bedside checklist 2. Audit and feedback: weekly manual compliance audits 3. Education events: monthly presentations with written and electronic materials	Old guidelines	313	368	After implementation of the VTE protocol, more patients received anticoagulation (pre: 39.4%, post: 80.5%, p<0.001), time to initiation was shorter (pre:140 hours, post: 59 hours, p<0.001), and there were fewer VTE events (pre: 19 (5.2%), post: 7 (2.2%), p=0.047)	Combining education and multifaceted protocol implementation can help organizations to better focus limited quality resources and counteract barriers that have hindered adoption of best practices

AIS, Abbreviated Injury Scale; CDS, Clinical Decision Support; CPG, clinical practice guideline; CPOE, computerized provider order entry; DVT, deep venous thrombosis; ICU, intensive care unit; TBI, traumatic brain injury; VTE, venous thromboembolism.

cost of care. Engels *et al*[16] reported on mortality in patients seen by the thrombosis service; however, the improved mortality in patients seen by the thrombosis service was not statistically significant (2.4% vs. 4.5%, p=0.2). There were no significant differences in reported ICU LOS (9.5 vs. 9.0 days, p=0.7) or in overall LOS (13.1 vs. 12.2 days, p=0.6). Tignanelli and colleagues[17] reported no statistically significant differences in complications, mortality, or hospital LOS. However, patients in the active implementation strategy group had significantly fewer ventilator days (OR=0.71, p=0.002).

Grading the evidence

Among the studies included in our review, none were randomized, three were entirely retrospective, and one had retrospective and prospective components. As such, the risk of bias was high. Limitations of studies are described in table 2. There was heterogeneity in the type of trauma patient population included and in the implementation strategies used. In the pooled analysis, heterogeneity was high for the outcome of patients who received VTE prophylaxis (I^2=86%) and moderate for VTE events (I^2=57%). For the proportion of patients who received thromboprophylaxis, inconsistency was low based on the positive effect of the intervention in each of the studies. There was a low concern for indirectness as the studies directly measured the outcomes in question. Imprecision was serious due to a wide CI and the small number of included studies. For VTE events, there were concerns for inconsistency and imprecision based on a wide CI. Indirectness was low due to direct measures of VTE outcomes. Overall, the quality of evidence was low for the proportion of patients who received VTE prophylaxis and very low in VTE events outcomes (summarized in table 3).

DISCUSSION

VTE is a leading cause of preventable morbidity and mortality in trauma patients, and routine thromboprophylaxis is recommended by CPGs for these patients. In spite of this, we were only able to find four heterogeneous studies that assessed the impact of active interventions to increase thromboprophylaxis use in trauma patients, none of which were randomized trials. This represents a major gap in trauma patient care and at least in part reflects the variability in thromboprophylaxis in these patients.

Our review did show a significant increase in the proportion of patients who received VTE prophylaxis by utilizing one or

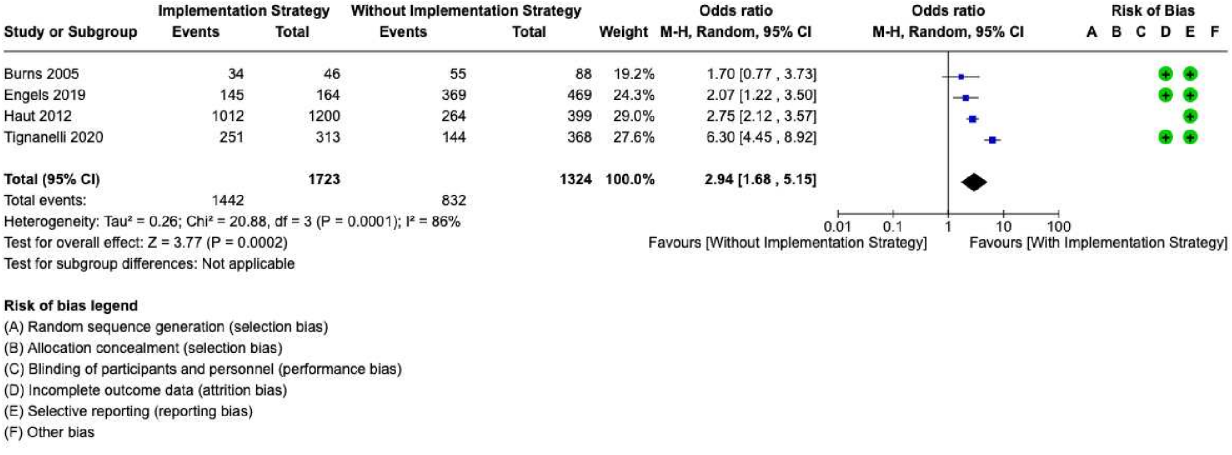

Figure 2 Analysis of patients who received venous thromboembolism prophylaxis.

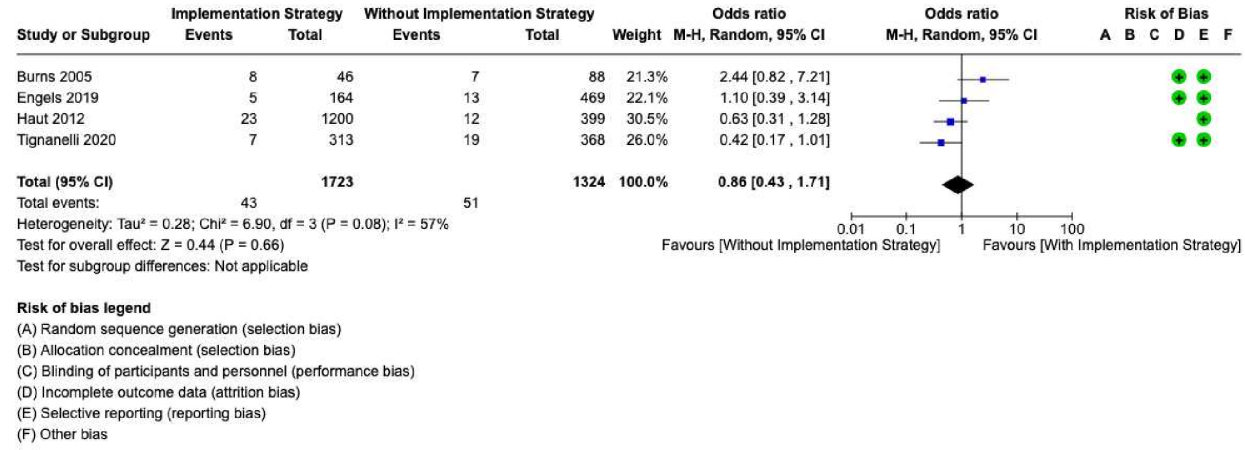

Figure 3 Analysis of venous thromboembolism events.

more active implementation strategies. However, we were not able to demonstrate a significant difference in VTE events.

Our results are congruent with previous studies published on hospitalized medical and surgical patients including systematic reviews by Kahn *et al*[11 12] and Tooher *et al*.[19] These studies have also demonstrated the positive effect of active implementation strategies to remind and assist clinicians in the selection of appropriate anticoagulant VTE prophylaxis.[20–27] Our focus on hospitalized trauma patients was motivated by the relatively high risk of VTE, as well as the morbidity and mortality associated with VTE in the trauma population.[1 2] Although some studies combined surgical, trauma, and medical patients, we were not able to differentiate the demographics or outcomes that are relevant to trauma patients.[28–30] Gallagher *et al* [29]described the implementation of a VTE prophylaxis guideline using active strategies that included education and creation of a risk assessment tool for all hospitalized medical and surgical patients. In examining 318 VTE events prospectively over 3.5 years, the authors concluded that utilizing active implementation strategies improved the use of prophylaxis and may reduce VTE events. Cassidy *et al*[30] described the creation of a mandatory risk-stratified electronic order entry system, a mobilization program, and audit and feedback for VTE prophylaxis implementation in all surgical patients and demonstrated a decrease in the incidence of VTE by 84%. However, the demographics and outcomes of trauma surgical patients were not delineated in these studies. Kahn *et al*[11] demonstrated that several types of implementation strategies can be effective; however, a multifaceted approach had the greatest effect. The success of these interventions can be attributed to factors such as improved healthcare provider awareness, adherence to a specific protocol, and enhanced provider (and sometimes patient) engagement. Active strategies such as electronic and human alerts facilitate timely and informed decision-making, contributing to the improved compliance observed in this study.

We were not able to demonstrate that multifaceted implementation strategies prevented VTE in our review, although such benefit has been demonstrated in other patient groups.[15 23 26 29 31–35] However, the current body of implementation research varied with respect to the type of VTE (asymptomatic vs. symptomatic, or proximal vs. distal DVT) and does not describe bleeding complications, HIT, or cost of care associated with implementation strategies. There are several national societal guidelines to guide appropriate VTE prophylaxis in trauma patients.[6–8] Furthermore, VTE is measured as a benchmark for quality by The Trauma Quality Improvement Program. VTE prevention was ranked number 1 of 79 methods to improve patient safety in hospitals and is listed as a top 10 patient safety practice according to the Agency for Healthcare Research and Quality (AHRQ).[36 37] Despite the clear quality implications, it is not known which implementation strategies are being used across trauma centers in North America and elsewhere. Future studies should focus on the system-wide implementation strategies being used in trauma centers and which ones demonstrate the greatest impact on clinically important outcomes.[38] Furthermore, studies are required to understand why some implementation strategies do not appear to reduce VTE events despite increasing the proportion of patients receiving VTE prophylaxis. Questions regarding appropriate modalities of prophylaxis, initiation times, and adherence to optimal doses should be accounted for. In clinical practice, factors that hinder the provision of VTE prophylaxis to trauma patients are numerous and complex. Challenges that trauma centers may face include heterogeneous injury burden, the lack of standardized protocols, and, perhaps, suboptimal institutional support. These challenges underscore the importance of tailored interventions that fit within existing workflows and minimize disruptions.

Limitations

Our meta-analysis has important limitations. The extensive search screened more than 7000 studies; however, only four studies met our inclusion criteria. This scarcity underscores the paucity of research specifically investigating VTE prophylaxis implementation in trauma patients and limits our ability to analyze the 'best' implementation strategy to reduce VTE events. The non-randomized, retrospective assessment of the intervention groups introduces potential biases and confounding that may influence observed outcomes. Heterogeneity in patient populations, healthcare settings, and implementation strategies across the selected studies further impacts generalizability. Studies examining outcomes such as bleeding complications, LOS, and healthcare costs were not found, further underscoring the need for the study of VTE implementation strategies and relevant outcomes. Although this review provides valuable insights into VTE prophylaxis implementation in trauma patients, its limitations highlight the need for further research to address gaps, enhance intervention quality, and improve real-world applicability.

Table 2 Certainty of evidence assessment

Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no active implementation strategies	With active implementation strategies		Risk with no active implementation strategies	Risk difference with active implementation strategies
Proportion of patients who received VTE prophylaxis											
3047 (4 observational studies)	Serious	Not serious	Not serious	Serious	None	⊕⊕ Low	832 of 1324 (62.8%)	1442 of 1723 (83.7%)	OR 2.94 (1.68 to 5.15)	628 per 1000	204 more per 1000 (from 111 more to 269 more)
VTE events											
3047 (4 observational studies)	Serious	Serious	Not serious	Serious	None	⊕ Very low	51 of 1324 (3.9%)	43 of 1723 (2.5%)	OR 0.86 (0.43 to 1.71)	39 per 1000	5 fewer per 1000 (from 22 fewer to 26 more)

VTE, venous thromboembolism.

Table 3 Possible limitations identified in each study

Study	Limitations to consider
Burns *et al*[18]	▶ Studied SCI patients at specialized SCI centers ▶ It is unclear whether improved adherences reflected in improved care or only in documentation ▶ Method of VTE diagnosis not clear ▶ Complications of VTE prophylaxis administration and length of stay not presented
Haut *et al*[15]	▶ Retrospective review, single-center study ▶ Was not powered to demonstrate statistical significance in VTE events ▶ Surveillance bias with protocol in place to screen high-risk asymptomatic patients
Engels *et al*[16]	▶ Retrospective review, single-center study ▶ Longitudinal VTE prophylaxis administration was not measured ▶ Complications of VTE prophylaxis not captured
Tignanelli *et al*[17]	▶ Retrospective review, single-center study ▶ Studied only TBI patients ▶ Low mortality and complications in patients who received VTE prophylaxis may not be reflective of TBI population due to inclusion of only patients who received VTE prophylaxis and may indicate a selection bias

TBI, traumatic brain injury; VTE, venous thromboembolism.

CONCLUSIONS

Active implementation strategies improve the proportion of patients who received VTE prophylaxis. Although it is unclear which is the 'best' implementation approach, we recommend that trauma centers adopt active implementation strategies to ensure high adherence to evidence-based guidelines. The role of implementation science, a critically important aspect of trauma research, cannot be overlooked.[39 40] Further studies are needed to analyze the best strategies for a cost-effective and sustainable approach to VTE prevention and to understand related outcomes such as bleeding and cost.

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Contributors AR, SSS, and EH contributed to literature search; AR, WG, and PM to study design; AR, SSS, MC, AG, and KP to data collection; AR, WG, and PM to data analysis; AR, EH, ERH,WG, and PM to critical revision; AR is the guarantor.

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