Published in final edited form as:

J Trauma Acute Care Surg. 2023 March 01; 94(3): 479–483. doi:10.1097/TA.0000000000003853.

Novel Therapeutic Medications for Venous Thromboembolism Prevention in Trauma Patients: Findings from the Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma

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Abstract

Trauma patients are at high risk for venous thromboembolism (VTE). Despite evidence-based guidelines and concerted efforts in trauma centers to implement optimal chemoprophylaxis strategies, VTE remains a frequent diagnosis in trauma patients. Current chemoprophylaxis strategies focus largely on the subcutaneous injection of low molecular weight heparin which is administered twice daily. Novel approaches to pharmacologic VTE prophylaxis have the potential to reduce VTE rates by improving patient compliance through oral administration or through their ability to target alternative pathways that mediate thrombosis. While novel pharmacologic VTE

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Author Contributions:
Literature search: NKD, ALT, EJL
Writing: NKD, ERH, TWC, ALT, EJL
Critical revision: MAP, BAC

Conflicts of Interest Statement:
The authors have no conflicts of interest to disclose.

prophylaxis strategies have been studied in non-trauma patients, there is a paucity of literature in trauma patients where the risk of thrombosis versus hemorrhage must be carefully considered. As a component of the 2022 Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma, this review provides an update of the novel chemoprophylaxis agents for potential use in trauma patients. Here, we will consider the relative risks and benefits related to the use of these drugs, evaluate the current literature in non-trauma patients, and consider future directions that could potentially improve post-trauma VTE prophylaxis.

Introduction

Recent advances in the approach to optimizing venous thromboembolism (VTE) prophylaxis in trauma patients, including early initiation and higher doses of chemoprophylaxis, have led to lower VTE rates.[1,2] VTE prevention after trauma requires vigilance and focused measures to mitigate their development. Despite successful efforts to optimize chemoprophylaxis strategies, VTE events continue to occur with unacceptable frequency in injured patients. While subcutaneous administration of low molecular weight heparin (LMWH) is standard of care, further research is needed to better understand the role and efficacy of alternative chemoprophylactic agents which have the potential to revolutionize current VTE prevention strategies in trauma patients.

Alternative agents for pharmacologic VTE prophylaxis may be suitable for use in trauma patients and could potentially be advantageous compared to current heparin-based regimens. Oral agents including aspirin and direct oral anticoagulants (DOACs), such as rivaroxaban or apixaban, are currently the leading candidates for use as novel chemoprophylactic agents. While these drugs may be ideal due to ease of administration via the oral route, issues with prolonged half-life, inability to rapidly reverse their anticoagulant effects, and overall risk of bleeding are concerns when use in trauma patients is considered. Unfortunately, randomized clinical studies in trauma patients have been limited.

The 2022 Consensus Conference to Implement Optimal Venous Thromboembolism (VTE) Prophylaxis in Trauma was convened to define evidence-based guidelines and to address gaps in clinical care and research related to VTE.[3] One of the defined goals of this conference was to discuss novel approaches to post-injury VTE prophylaxis that could potentially improve patient compliance and further decrease VTE risk. The aim of this review is to discuss drugs that could be utilized as novel chemoprophylaxis agents for use in trauma patients, identify benefits and risks related to use of these drugs, evaluate the current literature in non-trauma patients and consider future directions that could allow improvements in post-trauma VTE prophylaxis.

Current Strategies in VTE Chemoprophylaxis

While specific VTE prophylaxis strategies vary by institution, there are recent consensus, evidence-based guidelines from the Western Trauma Association, the American Association for the Surgery of Trauma, and the American College of Surgeons – Committee on Trauma that provide recommendations to achieve optimal VTE prophylaxis after trauma.[4,5] The two typical agents used for chemoprophylaxis are unfractionated heparin (UH) or

LMWH. LMWH is recommended over UH in most trauma patients given its superior pharmacokinetic properties in terms of bioavailability and longer half-life.[6] Additionally, concerns for complications such as heparin induced thrombocytopenia (HIT) occur rarely with LMWH.[7] Higher doses of LMWH may be needed to achieve appropriate prophylaxis, with recent consensus guidelines now recommending enoxaparin 40mg twice daily as the initial dose in most trauma patients..[8] LMWH is currently not recommended for all patients. Impaired renal clearance associated with acute kidney injury or chronic renal failure is a common reason to utilize UH as the chemoprophylactic agent of choice.

Challenges with Current VTE Chemoprophylaxis Strategies

While improvements have been made in the timing of initiation and dosing of VTE prophylaxis, there are a number of limitations with current chemoprophylaxis dosing regimens. Perhaps the most obvious limitation is that patients receive a painful subcutaneous injection of the medication which can lead to patient dissatisfaction, noncompliance, and missed doses of VTE prophylaxis. Haac et al. performed a randomized controlled trial wherein orthopedic trauma patients were discharged from the hospital with either aspirin 81mg twice daily or LMWH 30mg twice daily.[9] Patients were contacted between 10 to 21 days after discharge and adherence scores were measured. While adherence was overall high, LMWH was associated with a lower rate of adherence, even when adjusted for age, sex, health insurance status, and if the agent was administered by a provider.

Varied rates of adherence with current chemoprophylaxis may stem from the fact that patients generally prefer oral options over subcutaneous injections. Of 227 patients surveyed about VTE prophylaxis preferences, 60.4% preferred oral medications provided that they were equally as effective as subcutaneous alternatives.[10] Subcutaneous injections of LMWH or UH for VTE prophylaxis are one of the most commonly refused medication in hospitalized patients.[11,12] However, it would be too simple to state that patients only prefer oral agents under any circumstance. Haac and colleagues performed a discrete choice experiment on trauma patients at their Level 1 trauma center where they gave patients different, hypothetical scenarios and gauged preferences accordingly.[13] While patients generally favored oral agents, subcutaneous agents were preferred when certain statistics were given for complications such as bleeding, VTE, and death. This finding suggests that preferences may change based on risk-based information provided to patients, however, it is unclear understanding the risks of refusing subcutaneous chemoprophylaxis results in changes in behavior and increased compliance.

Additionally, cost needs to be considered when delivering VTE chemoprophylaxis. Older studies cite substantially higher costs with LMWH compared to alternatives although without considering the increased HIT rate with UH.[14,15] The cost-effectiveness of current management strategies for VTE chemoprophylaxis in trauma patients require additional analysis.

As Simple as Aspirin?

Salicylates have solidified their presence in medical history for centuries, with acetylsalicylic acid, commonly known as aspirin, being introduced in the 1890s.[16] Aspirin irreversibly inactivates cyclooxygenase enzyme which is required for thromboxane and prostaglandin synthesis, leading to impaired platelet aggregation (Table 1).

The literature regarding platelet physiology and pathophysiology following injury has been growing over the last decade. Thromboelastography with platelet mapping has suggested that platelets play a significant role in trauma-induced hypercoagulability.[17,18] Platelet dysfunction is implicated in microthrombotic disease after trauma, however its role in VTE formation is unknown.[19,20] Matthay and colleagues examined several coagulation parameters among patients with and without VTE.[21] The authors found that patients with impaired platelet aggregation had a higher risk of developing VTE, suggesting that platelet dysfunction may play a role in VTE formation.

Clinical studies evaluating the efficacy of aspirin for VTE chemoprophylaxis in the general trauma population are limited. Brill et al performed a retrospective case-control study where patients with lower extremity DVTs were matched by demographics, injury characteristics, probability of death, and other DVT risk factors.[22] Preinjury aspirin use was found to be protective against VTE. This association was more pronounced when a heparinoid chemoprophylaxis was administered during the patient's hospital admission. This may be because heparinoid agents and antiplatelet agents act on different targets which are necessary for thrombin and clot formation. In contrast, another study determined that prehospital aspirin was a predictor for increased risk of VTE, possibly due to a rebound in platelet physiology.[23]

To better understand the potential benefits of aspirin as VTE chemoprophylaxis in trauma patients, the orthopedic literature provides some guidance. One of the largest studies to date regarding aspirin use is a retrospective cohort study using a large quality initiative registry of 41,537 patients undergoing total knee arthroplasty from 29 hospitals in Michigan.[24] Aspirin alone was compared to other anticoagulants including LMWH, warfarin, and factor Xa inhibitors, an anticoagulant in addition to aspirin, and no agents at all. The authors demonstrated that aspirin was noninferior to other anticoagulants with respect to VTE prophylaxis and proposed that it may be a suitable alternative for pharmacologic prophylaxis. Additionally, aspirin is generally preferred by orthopedic surgeons due to a lower risk of bleeding and wound complications.[25,26] These studies have been instrumental in establishing guidelines which include aspirin as the chemoprophylactic agent of choice for certain orthopedic surgery patients.[27] The question then becomes if this regimen can be used for trauma patients with orthopedic injuries which was the premise for the A Different Approach to Preventing Thrombosis (ADAPT) trial.[28]

The ADAPT trial was a single-center prospective randomized controlled trial comparing aspirin twice daily to LMWH in orthopedic trauma patients at a Level 1 trauma center (Table 2). The study included trauma patients with an operative extremity, hip, or acetabular fracture. Those randomized to LMWH could undergo dose adjustments guided by body

mass index or factor Xa activity. The investigators sought to determine the probability of treatment superiority with LMWH over aspirin by using a combination of statistical methods. There were no statistical differences in the VTE rate when LMWH was compared to aspirin in this study. The ADAPT trial provided insight in how aspirin may be used as chemoprophylaxis in trauma patients with specific orthopedic injuries and introduced the potential for aspirin use in a wider variety of trauma patients.

The results of PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT), a multicenter randomized trial with over 12,000 patients admitted to 21 centers will provide clarity.[29] The study, which includes orthopedic trauma patients with and without additional injuries, compares aspirin and LMWH and aims to determine outcome differences with respect to mortality, PE, DVT, and additional safety outcomes including bleeding, and wound complications.

DOACs as Novel Prophylactic Agents

DOACs, are increasingly prescribed in the general medical population. DOACs can be used for a number of medical conditions such as VTE, mechanical valves, stroke prevention, and in select patients with vascular disease.[30] Dosing with DOACs is relatively easier to accomplish compared to traditional anticoagulants, thus making it a more attractive option for both providers and patients.

The Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial intended to establish DOACs as a viable option for VTE prevention.[31] In this international, multi-center, double-blinded, randomized controlled trial, medical patients received either apixaban 2.5mg twice daily or enoxaparin 40mg once daily for 6 to 14 days. These medical patients included individuals who were admitted for at least three days with congestive heart failure, respiratory failure, infection, acute rheumatic disorder, or inflammatory bowel disease. While the investigators initially hypothesized that apixaban would be superior, they saw similar VTE outcomes and observed more bleeding events with apixaban.

The Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin (MAGELLAN) was published in 2013 and compared an extended course of rivaroxaban to enoxaparin in medical patients.[32] The study was designed to detect both symptomatic and asymptomatic VTE by screening all patients after receiving the last dose of medication. With over 8,000 patients enrolled, extended administration of rivaroxaban for 35 days was found to reduce VTE risk. However, similar to apixaban in the ADOPT trial, rivaroxaban was associated with a higher bleeding risk.

The role of DOACs in surgical patients requires investigation given the observed bleeding risk in the aforementioned studies. Similar to aspirin, most relevant data originate from the orthopedic surgery literature. Eriksson et al conducted a phase 3 trial (RECORD1) comparing rivaroxaban 10mg once daily to enoxaparin 40mg once daily in patients undergoing total hip arthroplasty.[33] Patients randomized to rivaroxaban had fewer VTEs. This study was followed by RECORD3, by Lassan et al., which studied rivaroxaban

compared to enoxaparin in patients following total knee arthroplasties.[34] Rivaroxaban was superior to enoxaparin in preventing VTE and unlike other trials, was associated with similar bleeding events. The frequency of drug related complications was also similar.

While the aforementioned studies show that DOACs are potential alternatives for VTE prophylaxis in surgical patients, they lend little insight into how DOACs can be specifically used in the trauma population. A single-center propensity matched study at a Level 1 trauma center showed that patients given rivaroxaban for VTE prophylaxis had similar rates of VTE compared to those that received enoxaparin.[35] It is important to note the injury profiles represented in this study as approximately one in three patients had severe injuries to the head and/or neck. Additionally, there were fewer patients with severe chest and abdominal injuries in the rivaroxaban cohort despite the patients being matched. Another propensity matched study focused on trauma patients with lower extremity fractures using the American College of Surgeons - Trauma Quality Improvement Program database.[36] Before matching, patients who were given DOACs had lower rates of traumatic brain injury, rib, pelvic, and spinal fractures but had a substantially higher rate of femur fractures. The VTE rate was similar with a slightly lower need for bleeding control interventions, but this did not reach statistical significance.

Prospective studies investigating DOAC use in trauma patients are absent. Future studies are needed to understand which patients would benefit from this class of drugs, in addition to their safety profiles and efficacy.

Future Directions

While the foundational research has established the potential for aspirin and DOAC use as possible alternatives for chemoprophylaxis in trauma patients, additional studies are needed before these agents can be recommended and included in the related practice guidelines.

If the PREVENT CLOT study demonstrates that aspirin is as equally effective as LMWH, questions will inevitably arise about the optimal dosing of aspirin and LMWH. The study randomized patients to aspirin 81mg twice daily. Does daily dosing or aspirin 325mg have differing results? If aspirin is not superior to LMWH, would adding aspirin to LMWH provide an advantage? How does optimal dosing of aspirin compare to optimal dosing of LMWH? Can the same results apply to trauma patients without orthopedic injury? Each of these questions should be potentially addressed in future clinical research studies.

The heterogeneity of injury patterns and bleeding risk after major trauma make generalized recommendations regarding the optimal novel chemoprophylactic strategy difficult to define and implement. There are challenges with initiating and dosing chemoprophylaxis in trauma patients with traumatic brain injury, spinal injury, and solid organ injuries even with current regimens.[37-39] Establishing that oral agents are safe in these specific injuries and in patients with polytrauma will require further studies.

Another added challenge is the issue of enteral access, bioavailability, and related pharmacokinetics. Injuries to the gastrointestinal tract, ileus, bowel obstruction, and inability to take medications *per os* may preclude individuals from taking aspirin or a DOAC. While

aspirin can alternatively be delivered rectally, which in itself has added challenges, DOACs cannot.

Conclusions

Although the trauma community has made substantial improvements in VTE prevention with contemporary practices, there are limitations with current standards. Alternative agents, namely aspirin and DOACs, may serve as suitable alternatives. While literature exists for the appropriateness of these agents outside of trauma, more research is required to establish their efficacy and safety in trauma patients.

Disclosures of Funding:

Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R13HL158206 (“Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma”). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Dr. Haut reports research funding from The Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality (AHRQ), the NIH/NHLBI, and the DOD/Army Medical Research Acquisition Activity.

Dr. Haut reports research funding from The Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality (AHRQ), the NIH/NHLBI, and the DOD/Army Medical Research Acquisition Activity.

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Table 1:

Properties of Potential Novel Therapeutics

Agent	Mechanism of action	Formulations	Prophylactic Dosing Investigated	Bioavailability	Half-Life	Metabolism/ elimination
Aspirin	Inactivates cyclooxygenase enzyme	Per os or per rectum	81mg twice daily	50-75%	15-20 minutes (however effects of aspirin last the duration of platelet life which is approximately 10 days)	Metabolized in plasma and liver; excreted through kidney
Apixaban	Directly binds to Factor Xa	Per os	2.5mg twice daily	50%	12 hours	Metabolized by liver; excreted through kidney, biliary, and fecal
Rivaroxaban	Directly binds to Factor Xa	Per os	10mg once daily	80%-100%	5-9 hours	Metabolized by liver; excreted through kidney

Table 2:

Summary of Prospective Trials Using Potential Novel Therapeutics

Agent	Study Name	Study Design	Patient Population	Summary
Aspirin	ADAPT: A Different Approach to Preventing Thrombosis	Single-center, randomized control trial	Orthopedic trauma patients	LMWH 30mg twice daily had a 50.4% (95% CI, 47.7-53.2%, p=0.73) probability of superiority over aspirin 81mg twice daily using a Global Rank test
	PREVENT CLOT: PREVENTion of Clots in Orthopaedic Trauma	Multicenter, randomized control trial	Orthopedic trauma patients	Published results pending
Apixaban	ADOPT: Apixaban Dosing to Optimize Protection from Thrombosis	Multicenter, randomized controlled trial	Medical patients hospitalized with congestive heart failure, acute respiratory failure, infection, acute rheumatic disorder, or inflammatory bowel disease	Apixaban 2.5mg twice daily for 30 days was similar to LMWH 40mg once daily for 6 to 14 days with respect to VTE; major bleeding occurred more frequently in the apixaban arm (relative risk, 2.58; 95% CI, 1.02-7.24, p=0.04).
Rivaroxaban	MAGELLAN: Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin	Multicenter, randomized controlled trial	Medical patients hospitalized with acute illness	Rivaroxaban 10mg once daily was noninferior to enoxaparin 40mg once daily (relative risk, 0.97; 95% CI: 0.71-1.31), p<0.01 for noninferiority).
	RECORD 1: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty	Multicenter, randomized controlled trial	Patients undergoing elective total hip arthroplasty	Rivaroxaban 10mg once daily was more effective than LMWH 40mg once daily (absolute risk reduction for DVT, nonfatal PE, or death 2.6%, 95% CI 1.5%-3.7%, p<0.01).
	RECORD 3: Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty	Multicenter, randomized controlled trial	Patients undergoing total knee arthroplasty	Rivaroxaban 10mg once daily was superior to enoxaparin 40mg once daily (absolute risk reduction for DVT, nonfatal PE, or death 9.2%; 95% CI 5.9%-12.4%, p<0.01).

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism