Recommendations from the ICM-VTE: Trauma

The ICM-VTE Trauma Delegates*

1 - What is the most optimal VTE prophylaxis in patients with multiple orthopaedic injuries?

Response/Recommendation: Although multiple forms of prophylaxis against venous thromboembolism (VTE) with variable effectiveness are available for patients with multiple orthopedic injuries, low-molecular-weight heparin (LMWH) is considered the most optimal choice based on available literature.

Strength of Recommendation: Acceptable.

Delegates vote: Agree 86.36% Disagree 9.09% Abstain 4.55% (Strong Consensus).

Rationale: VTE events following multiple orthopaedic injuries are associated with significant morbidity and mortality[1,2]. The prevalence of deep venous thrombosis (DVT) in trauma patients without prophylactic treatment can reach up to 60%. Pulmonary embolism (PE) can be a fatal form of VTE with prevalence ranging between 2 - 16%[3,4]. VTE can be prevented using different mechanical and chemical prophylaxis agents, therefore, significantly lower the burden on healthcare systems worldwide[1]. The aim of this review is to find the most optimal VTE prophylaxis in patients with multiple orthopaedic injuries.

Multiple orthopaedic injuries rarely happen without extra-skeletal injuries, therefore, no studies in the current literature addressed VTE prophylaxis in patients with multiple orthopaedic injuries but without extra-skeletal injuries. Most of the available literature is addressing this patient population under different groups including, patients with trauma, poly-trauma, high energy fractures and lower extremity injuries[1-3,5-7]. The level of evidence varies among the reviewed literature, however, randomized controlled clinical trials in this subject are limited[3,4].

Based on our review, LMWH is considered the most optimal VTE prophylaxis in patients with multiple orthopaedic injuries[1,3,5,6,8-14]. Ley et al., recommends using LMWH due to its increased bioavailability, acceptably low bleeding complications and longer plasma half-life[1]. Rogers et al., published in their guidelines for prevention of VTE in trauma patients that LMWH has superior bioavailability when compared to low-dose heparin (LDH)[5]. Knudson et al., concluded in a prospective, randomized trial that LMWH is an extremely effective and safe method in preventing DVT in high-risk trauma patients[15]. Geerts et al., also concluded in a randomized double blinded study that LMWH was more effective than LDH in preventing VTE after major trauma[16]. Aggarwal et al., concluded in their guidelines for prevention of VTE in hospitalized patients with pelvis and acetabular fractures that LMWH is the preferred agent of choice[8].

In the updated Western Trauma Association (WTA) guidelines to reduce VTE in trauma patients[1], LMWH was the recommended agent of choice for most trauma patients with a standard dose of 40 mg subcutaneously twice daily. However, in some cases such as obese patients, they recommended weight-based dosing at 0.5 mg to 0.6 mg/kg twice daily[1]. Timing of administration of LMWH is critical to achieve the optimal prophylaxis desired. It should be given to patients as soon as risk of bleeding is low to avoid complications[1,3,11,17]. According to Ley et al., pharmacologic prophylaxis should be started as soon as possible within 24 hours after injury[1].

Fondaparinux[18] is a synthetic penta-saccharide drug that potentiates activity of antithrombin III that inhibits factor Xa. With a common dosage of 2.5 mg daily subcutaneously, this chemical prophylaxis showed promising results in elective orthopaedic surgery such as arthroplasty[19]. However, several issues have been raised to debate its safety in trauma patients[18,20]. Therefore, further studies are required to prove its safety and efficacy in trauma[5].

Another method of prophylaxis is the use of mechanical prophylaxis in form of pneumatic compression devices (PCD) which was promoted by the Eastern Association for the Surgery of Trauma (EAST) work group practice management guidelines for the prevention of VTE in trauma patients[3], especially in patients where chemical prophylaxis is contraindicated[1,6-8,21]. PCD can be used as an adjunct with chemical prophylaxis in moderate and high-risk patients[1,10,22,23]. The combination has shown lower incidence of symptomatic PE according to Ley et al[1]. High-risk patients include those with hemodynamic instability, active bleeding, and head trauma[1,5,8]. The use of mechanical prophylaxis without chemical prophylaxis in the absence of contraindication to chemical prophylaxis is not recommended according to multiple studies[2,7].

*A list of the ICM-VTE Trauma Delegates is included in a note at the end of the article.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G855).

Inferior vena cava (IVC) filters are another form of prophylaxis against VTE[4,24], although they are not without risk. It has an established role as an adjunct to LMWH in patients with DVT to prevent PE[8]. However, multiple studies recommend the use of IVC filters to be reserved for patients who cannot receive any form of prophylaxis or patients undergoing urgent surgery[5,6,25]. Khansarinia et al., concluded that insertion of IVC filter in multiply injured high-risk patients contributed to lower incidence and mortality rates of fatal and non-fatal PE[24].

Abdulaziz N. Aljurayyan, Ahmed A. Alabdali, Ryan K. Harrison

References

1. Ley EJ, Brown CVR, Moore EE, Sava JA, Peck K, Ciesla DJ, Sperry JL, Rizzo AG, Rosen NG, Brasel KJ, Kozar R, Inaba K, Martin MJ. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg. 2020 Nov;89(5):971-81.

2. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun; 133(6)(Suppl):381S-453S.

3. Toker S, Hak DJ, Morgan SJ. Deep vein thrombosis prophylaxis in trauma patients. Thrombosis. 2011;2011:505373.

4. Slobogean GP, Lefaivre KA, Nicolaou S, O'Brien PJ. A systematic review of thromboprophylaxis for pelvic and acetabular fractures. J Orthop Trauma. 2009 May-Jun;23(5):379-84.

5. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. J Trauma. 2002 Jul; 53(1):142-64.

6. Chana-Rodríguez F, Mañanes RP, Rojo-Manaute J, Haro JAC, Vaquero-Martín J. Methods and Guidelines for Venous Thromboembolism Prevention in Polytrauma Patients with Pelvic and Acetabular Fractures. Open Orthop J. 2015 Jul 31;9:313-20.

7. Niikura T, Sakai Y, Lee SY, Iwakura T, Kuroda R, Kurosaka M. Rate of venous thromboembolism after complex lower-limb fracture surgery without pharmacological prophylaxis. J Orthop Surg (Hong Kong). 2015 Apr;23(1):37-40.

8. Aggarwal S, Patel S, Vashisht S, Kumar V, Sehgal IS, Chauhan R, Chaluvashetty DSB, Hemanth Kumar DK, Jindal DK. Guidelines for the prevention of venous thromboembolism in hospitalized patients with pelvi-acetabular trauma. J Clin Orthop Trauma. 2020 Nov-Dec;11(6):1002-8.

9. Wang H, Chen W, Su Y, Li Z, Li M, Wu Z, Zhang Y. Thrombotic risk assessment questionary helps increase the use of thromboprophylaxis for patients with pelvic and acetabular fractures. Indian J Orthop. 2012 Jul;46(4):413-9.

10. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

11. Jehan F, O'Keeffe T, Khan M, Chi A, Tang A, Kulvatunyou N, Gries L, Joseph B. Early thromboprophylaxis with low-molecular-weight heparin is safe in patients with pelvic fracture managed nonoperatively. J Surg Res. 2017 Nov;219:360-5.

12. Ricci WM, Broekhuyse H, Keating JF, Teague DC, White TO. Thromboprophylaxis an update of current practice: Can we reach a consensus? OTA Int. 2019 Nov 22;2(4):e027.

13. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, Kelton JG. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med. 1995 May 18;332(20): 1330-5.

14. Byrne JP, Geerts W, Mason SA, Gomez D, Hoeft C, Murphy R, Neal M, Nathens AB. Effectiveness of low-molecular-weight heparin versus unfractionated heparin to prevent pulmonary embolism following major trauma: A propensity-matched analysis. J Trauma Acute Care Surg. 2017 Feb;82(2):252-62.

15. Knudson MM, Morabito D, Paiement GD, Shackleford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. J Trauma. 1996 Sep;41(3):446-59.

16. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5; 335(10):701-7.

17. Schellenberg M, Benjamin E, Inaba K, Heindel P, Biswas S, Mooney JL, Demetriades D. When Is It Safe to Start Pharmacologic Venous Thromboembolism Prophylaxis After Pelvic Fractures? A Prospective Study From a Level I Trauma Center. J Surg Res. 2021 Feb;258:272-7.

18. Tsiridis E, Gamie Z, George MJ, Hamilton-Baille D, West RM, Giannoudis PV. Early postoperative bleeding in polytrauma patients treated with fondaparinux: literature review and institutional experience. Curr Vasc Pharmacol. 2011 Jan;9(1): 42-7.

19. Lu JP, Knudson MM, Bir N, Kallet R, Atkinson K. Fondaparinux for prevention of venous thromboembolism in high-risk trauma patients: a pilot study. J Am Coll Surg. 2009 Nov;209(5):589-94.

20. Kanakaris NK, Nikolaou VS, Tosounidis T, Giannoudis PV. Fondaparinux for the prevention or treatment of venous thromboembolism related to lower limb trauma: evidence today. Curr Vasc Pharmacol. 2008 Apr;6(2):134-42.

21. Sekharan J, Dennis JW, Miranda FE, Hertz JA, Veldenz HC, Dovgan PS, Frykberg ER. Long-term follow-up of prophylactic greenfield filters in multisystem trauma patients. J Trauma. 2001 Dec;51(6):1087-90, discussion :1090-1.

22. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby G, Reddy DJ, Ntouvas I. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. Cochrane Database Syst Rev. 2016 Sep 7;9:CD005258.

23. Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. J Orthop Trauma. 1995 Feb;9(1): 1-7.

24. Khansarinia S, Dennis JW, Veldenz HC, Butcher JL, Hartland L. Prophylactic Greenfield filter placement in selected high-risk trauma patients. J Vasc Surg. 1995 Sep;22(3):231-5, discussion :235-6.

25. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004 Sep; 240(3):490-6, discussion :496-8.

2 - What is the optimal VTE prophylaxis for polytrauma patients with both fractures and visceral injuries?

Response/Recommendation: In patients with fractures and visceral injuries, anticoagulant-based thromboprophylaxis should be commenced as soon as bleeding risk allows. Bilateral mechanical thromboprophylaxis, if possible, should be administered to patients who are at high bleeding risk.

Strength of Recommendation: Strong.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Orthopaedic trauma patients frequently have concomitant visceral and/or brain injuries[26-29]. In general, major fractures significantly increase the risk of VTE in polytrauma[30-35] while non-orthopaedic injuries (except spinal cord injuries) generally have a much lower impact on the risk of VTE associated with fractures[36,37]. Conversely, bleeding risk in patients with polytrauma is largely dictated by the presence of visceral and brain injuries.

In polytrauma, VTE risk is relatively high[38,39], and use of mechanical and/or chemical prophylaxis should be considered[40-43]. However, there is wide variability in thromboprophylaxis practice among orthopaedic trauma centers at least in part because of the paucity of direct evidence in this specific group[44].

Timing of the initiation of anticoagulant thromboprophylaxis: In major trauma patients, the transition to a hypercoagulable state usually occurs early and is often seen at the time of admission[45-47]. Furthermore, numerous studies have shown that early initiation of anticoagulant thromboprophylaxis is associated with decreased risk of VTE in mixed trauma groups[27,28,37,43,44]

and in subgroups, including pelvic trauma[45-48], spine fractures[49-52], solid abdominal organ injuries[53-56], and head injuries[33,57,58]. At the same time, bleeding complications were not shown to be increased with early anticoagulant prophylaxis in most studies[33,37,43-46,48-55]. Among 2,752 patients with isolated, severe pelvic fractures, commencement of anticoagulant thromboprophylaxis within 48 hours after admission was associated with a 49% decrease in VTE, a 5-fold lower pulmonary embolism (PE) rate, and reduced mortality with no bleeding complications compared with later commencement[46]. However, patients who received early anticoagulant thromboprophylaxis had less severe injuries. Another study, that included 79,386 trauma patients, showed a significant decrease in VTE if thromboprophylaxis was started within the first 48 hours compared with a later start without an increase in bleeding events[44]. In this database study, most of the patients had an injury severity score (ISS) of less than 16 and neither distribution of fractures nor surgical management were reported. Rostas et al., found that early anticoagulant thromboprophylaxis in patients with blunt liver or spleen injuries was safe and was associated with reduced rates of VTE[43]. A double-blind randomized trial demonstrated the effectiveness and safety of low-molecular-weight heparin (LMWH) thromboprophylaxis started within 36 hours of injury in 344 major trauma patients; LMWH was also shown to be significantly more effective and as safe as low-dose heparin[59]. Another trial showed that, among trauma patients who were randomized to receive enoxaparin within 24 hours of admission or only mechanical thromboprophylaxis, major and minor bleeding did not differ between groups[60].

For patients with high risk of bleeding or in whom evidence of hemostasis has not yet occurred, the initial use of sequential compression devices (SCD) is recommended, although the evidence for use of SCD in major trauma is weak[35,36,61].

Traumatic brain injury patients: The main barrier to early anticoagulant thromboprophylaxis in patients with orthopaedic trauma is the presence of traumatic brain injury (TBI)[33,58,62]. Although patients with TBI have an increased risk of VTE[63,64], anticoagulant thromboprophylaxis is often delayed because of concerns about progression of intracranial bleeding (ICB). One study reported a greater risk of ICB associated with early anticoagulant thromboprophylaxis[65], while the vast majority did not[33,57,62,66-71]. Among 1,803 patients with moderate or severe TBI (head Abbreviated Injury Scale $\geq$ 2), those who started anticoagulant thromboprophylaxis within 48 hours after injury were three times less likely to develop VTE than those who started later without increased bleeding risk[33]. Three systematic reviews have each shown that VTE was significantly decreased with early anticoagulant thromboprophylaxis in TBI without an increased risk of ICB progression[67,72,73]. A possible limitation of most of the studies on this topic is that patients with the most severe head injuries may have been excluded or had delayed anticoagulant thromboprophylaxis. However, a large Trauma Quality Improvement Project (TQIP) study in 2,468 severe TBI patients used propensity-matching of those who had early (< 72 hours) or later (> 72 hours) anticoagulant thromboprophylaxis[57]. The early group had a lower risk of PE (odds ratio [OR], 0.48) and DVT (OR, 0.51) without an increase in either mortality or neurosurgical intervention. In the only randomized trial addressing this issue, enoxaparin started within 24 hours after injury in 681 TBI patients with stable head computer tomography (CT) was not associated with an increased risk of hemorrhagic progression compared with placebo[74]. Finally, a systematic review of 21 studies found no relationship between the timing of anticoagulant thromboprophylaxis initiation and hemorrhagic progression in patients with TBI[69].

The Neurocritical Care Society recommends that TBI patients commence anticoagulant thromboprophylaxis within 24 - 48 hours of presentation[75]. The American Association for the Surgery of Trauma (AAST) 2021 guidelines on VTE prophylaxis in TBI also recommend initiation of thromboprophylaxis as soon as possible, generally within 24 - 72 hours after admission[38]. We agree with early initiation of LMWH thromboprophylaxis in most TBI patients with the provision that a repeat head CT after the admission scan should demonstrate stability of intracranial bleeding. The presence of an intracranial pressure measurement device is not a contraindication to anticoagulant thromboprophylaxis[76].

Patients with solid organ injury: The majority of solid organ injuries (liver, spleen, kidney, and pancreas) are now treated nonoperatively[77]. Anticoagulant thromboprophylaxis started within 48 hours after blunt solid organ injury in addition to SCD was associated with significantly fewer DVT than a later start (0 vs. 9%, p = 0.024) with no patient requiring an intervention for bleeding[54]. The American College of Surgeons TQIP database was accessed to identify 36,187 patients with nonoperative solid organ injuries over a two-year period[55]. Patients who received thromboprophylaxis within 48 hours had significantly fewer DVT and PE than those who started later with no increase in bleeding complications or transfusion. These findings were confirmed in a subgroup analysis comparing a start of thromboprophylaxis within 24 hours compared to within 48 hours. Among 3,223 patients with isolated abdominal solid organ injuries, late initiation of anticoagulant thromboprophylaxis was an independent predictor of VTE (OR 3.2; 95% confidence interval [CI] 1.9 - 5.2) while abbreviated injury scale (AIS) scores of 3 - 5 for liver or spleen injuries were associated with increased bleeding rates regardless of timing of thromboprophylaxis[56]. The 2021 AAST guidelines recommend that LMWH start within 48 hours after solid organ injury if there is evidence that active bleeding has stopped[38]. This is based on multiple studies showing no increase in bleeding with early initiation of anticoagulant thromboprophylaxis in patients with solid organ injuries[43,54,55,78].

Conclusion: In polytrauma, the bleeding risk is highest immediately and in the early period after injury. Clearly, the initial clinical priority in such patients is to control active bleeding. The risk of VTE also begins early after injury although clinically important thrombosis is usually delayed. Both VTE and bleeding risks are modified by the combination of fractures and non-orthopaedic visceral injuries. Orthopaedic trauma

patients are at relatively high risk of VTE while the risk of bleeding is generally dictated by the concomitant visceral and head injuries. In general, delayed thromboprophylaxis is associated with increased VTE rates. At the same time, early initiation of anticoagulant thromboprophylaxis does not appear to be associated with increased bleeding risk in patients with visceral and head injuries when there is evidence that there is no active bleeding.

Recommendations:

1. We recommend that every polytrauma patient be evaluated on admission for both bleeding and thrombosis risks[37].
2. Patients with active bleeding are usually managed surgically or by endovascular embolization. We recommend that anticoagulant thromboprophylaxis be delayed until the high bleeding risk resolves.
3. Once there is evidence that there is no active bleeding, we recommend anticoagulant thromboprophylaxis, generally with weight-based LMWH and generally within 24 hours after injury[37]. For TBI, when consecutive brain imaging is stable for ICB (usually 24 - 36 hours after injury), we recommend starting anticoagulant thromboprophylaxis.
4. For patients at high risk for bleeding, we recommend starting SCD, although the high frequency of lower extremity fractures in polytrauma often precludes use of bilateral SCD. Once hemostasis occurs, we recommend replacing SCD with LMWH or adding LMWH to SCD.
5. We recommend early fixation of unstable fractures to reduce pain, promote mobility and decrease VTE risk[47]. If fracture repair will be delayed, we recommend that LMWH thromboprophylaxis not be delayed.
6. Since missed anticoagulant doses are associated with increased VTE risk, this should be avoided unless it is essential[33,78,79].
7. Early mobility and daily physiotherapy should also be encouraged[80,81]; for example, increased risk of DVT was seen after spinal injuries in which spinal precautions persisted beyond 72 hours compared with a shorter time in spite of routine use of SCD in both groups[82].
8. The duration of thromboprophylaxis in polytrauma is uncertain and is generally more influenced by orthopaedic and spinal cord injuries than by visceral injuries. We recommend that thromboprophylaxis generally be limited to the length of hospital stay.
9. For patients undergoing in-patient rehabilitation, we recommend continuation of thromboprophylaxis with either a direct oral anticoagulant such as rivaroxaban (generally our preference) or with LMWH. However, we recommend against post-discharge primary thromboprophylaxis unless there are additional major risk factors (such as previous VTE or active cancer); this approach has not been carefully studied and, therefore, is at the clinical judgement of the care team[83]. Further studies are underway[84].
10. We recommend the use of standardized VTE prophylaxis policies, embedded in routine order sets, as well as periodic audits of adherence to reduce unnecessary variability in practice and improve patient outcomes including VTE[37,38,85,86].

William H. Geerts, Abdulaziz N. Aljurayyan, Malin S. Carling

References

26. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004 Sep; 240(3):490-6, discussion :496-8.

27. Nathens AB, McMurray MK, Cuschieri J, Durr EA, Moore EE, Bankey PE, Freeman B, Harbrecht BG, Johnson JL, Minei JP, McKinley BA, Moore FA, Shapiro MB, West MA, Tompkins RG, Maier RV. The practice of venous thromboembolism prophylaxis in the major trauma patient. J Trauma. 2007 Mar;62(3):557-62, discussion :562-3.

28. Byrne JP, Geerts W, Mason SA, Gomez D, Hoeft C, Murphy R, Neal M, Nathens AB. Effectiveness of low-molecular-weight heparin versus unfractionated heparin to prevent pulmonary embolism following major trauma: A propensity-matched analysis. J Trauma Acute Care Surg. 2017 Feb;82(2): 252-62.

29. Karcutskie CA, Meizoso JP, Ray JJ, Horkan D, Ruiz XD, Schulman CI, Namias N, Proctor KG. Association of Mechanism of Injury With Risk for Venous Thromboembolism After Trauma. JAMA Surg. 2017 Jan 1;152(1):35-40.

30. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994 Dec 15; 331(24):1601-6.

31. 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 Aug; 73(2):511-5.

32. Domes CM, Schleyer AM, McQueen JM, Pergamit RF, Beingessner DM. Evaluation of Appropriate Venous Thromboembolism Prophylaxis in Patients With Orthopaedic Trauma With Symptom-Driven Vascular and Radiographic Studies. J Orthop Trauma. 2017 Dec;31(12):611-6.

33. Coleman JR, Carmichael H, Zangara T, Dunn J, Schroeppel TJ, Campion E, Goodman M, Hosokawa P, Sauaia A, Moore EE, Bunn B, Floren M, Ferrigno L. A Stitch in Time Saves Clots: Venous Thromboembolism Chemoprophylaxis in Traumatic Brain Injury. J Surg Res. 2021 Feb;258:289-98.

34. Valle EJ, Van Haren RM, Allen CJ, Jouria JM, Bullock MR, Schulman CI, Namias N, Livingstone AS, Proctor KG. Does traumatic brain injury increase the risk for venous thromboembolism in polytrauma patients? J Trauma Acute Care Surg. 2014 Aug;77(2):243-50.

35. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. Cochrane Database Syst Rev. 2013 Mar 28;(3):CD008303.

36. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. J Trauma. 2002 Jul; 53(1):142-64.

37. Ley EJ, Brown CVR, Moore EE, Sava JA, Peck K, Ciesla DJ, Sperry JL, Rizzo AG, Rosen NG, Brasel KJ, Kozar R, Inaba K, Martin MJ. Updated guidelines to reduce venous thromboembolism in trauma patients: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg. 2020 Nov; 89(5):971-81.

38. Rappold JF, Sheppard FR, Carmichael Ii SP, Cuschieri J, Ley E, Rangel E, Seshadri AJ, Michetti CP. Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document. Trauma Surg Acute Care Open. 2021 Feb 24;6(1):e000643.

39. Sagi HC, Ahn J, Ciesla D, Collinge C, Molina C, Obremskey WT, Guillamondegui O, Tornetta P 3rd; Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee. Venous Thromboembolism Prophylaxis in Orthopaedic Trauma Patients: A Survey of OTA Member Practice Patterns and OTA Expert Panel Recommendations. J Orthop Trauma. 2015 Oct;29(10):e355-62.

40. Selby R, Geerts W, Ofosu FA, Craven S, Dewar L, Phillips A, Szalai JP. Hypercoagulability after trauma: hemostatic changes and relationship to venous thromboembolism. Thromb Res. 2009 Jul;124(3):281-7.

41. Brill JB, Badiee J, Zander AL, Wallace JD, Lewis PR, Sise MJ, Bansal V, Shackford SR. The rate of deep vein thrombosis doubles in trauma patients with hypercoagulable thromboelastography. J Trauma Acute Care Surg. 2017 Sep;83(3): 413-9.

42. 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 Nov;85(5):907-14.

43. Rostas JW, Manley J, Gonzalez RP, Brevard SB, Ahmed N, Frotan MA, Mitchell E, Simmons JD. The safety of low molecular-weight heparin after blunt liver and spleen injuries. Am J Surg. 2015 Jul;210(1):31-4.

44. Hecht JP, Han EJ, Cain-Nielsen AH, Scott JW, Hemmila MR, Wahl WL. Association of timing of initiation of pharmacologic venous thromboembolism prophylaxis with outcomes in trauma patients. J Trauma Acute Care Surg. 2021 Jan 1;90(1):54-63.

45. Jehan F, O'Keeffe T, Khan M, Chi A, Tang A, Kulvatunyou N, Gries L, Joseph B. Early thromboprophylaxis with low-molecular-weight heparin is safe in patients with pelvic fracture managed nonoperatively. J Surg Res. 2017 Nov;219:360-5.

46. Benjamin E, Aiolfi A, Recinos G, Inaba K, Demetriades D. Timing of venous thromboprophylaxis in isolated severe pelvic fracture: Effect on mortality and outcomes. Injury. 2019 Mar;50(3):697-702.

47. Wu L, Cheng B. Analysis of perioperative risk factors for deep vein thrombosis in patients with femoral and pelvic fractures. J Orthop Surg Res. 2020 Dec 10;15(1): 597.

48. Schellenberg M, Benjamin E, Inaba K, Heindel P, Biswas S, Mooney JL, Demetriades D. When Is It Safe to Start Pharmacologic Venous Thromboembolism Prophylaxis After Pelvic Fractures? A Prospective Study From a Level I Trauma Center. J Surg Res. 2021 Feb;258:272-7.

49. Kim DY, Kobayashi L, Chang D, Fortlage D, Coimbra R. Early pharmacological venous thromboembolism prophylaxis is safe after operative fixation of traumatic spine fractures. Spine (Phila Pa 1976).) 2015 Mar 1;40(5):299-304.

50. Khan M, Jehan F, O'Keeffe T, Hamidi M, Truitt M, Zeeshan M, Gries L, Tang A, Joseph B. Optimal Timing of Initiation of Thromboprophylaxis after Nonoperative Blunt Spinal Trauma: A Propensity-Matched Analysis. J Am Coll Surg. 2018 May; 226(5):760-8.

51. Zeeshan M, Khan M, O'Keeffe T, Pollack N, Hamidi M, Kulvatunyou N, Sakran JV, Gries L, Joseph B. Optimal timing of initiation of thromboprophylaxis in spine trauma managed operatively: A nationwide propensity-matched analysis of trauma quality improvement program. J Trauma Acute Care Surg. 2018 Aug;85(2):387-92.

52. Hamidi M, Asmar S, Bible L, Hanna K, Castanon L, Avila M, Ditillo M, Joseph B. Early Thromboprophylaxis in Operative Spinal Trauma Does Not Increase Risk of Bleeding Complications. J Surg Res. 2021 Feb;258:119-24.

53. Joseph B, Pandit V, Harrison C, Lubin D, Kulvatunyou N, Zangbar B, Tang A, O'Keeffe T, Green DJ, Gries L, Friese RS, Rhee P. Early thromboembolic prophylaxis in patients with blunt solid abdominal organ injuries undergoing nonoperative management: is it safe? Am J Surg. 2015 Jan;209(1):194-8.

54. Schellenberg M, Inaba K, Biswas S, Heindel P, Benjamin E, Strumwasser A, Matsushima K, Lam L, Demetriades D. When is It Safe to Start VTE Prophylaxis After Blunt Solid Organ Injury? A Prospective Study from a Level I Trauma Center. World J Surg. 2019 Nov;43(11):2797-803.

55. Skarupa D, Hanna K, Zeeshan M, Madbak F, Hamidi M, Haddadin Z, Northcutt A, Gries L, Kulvatunyou N, Joseph B. Is early chemical thromboprophylaxis in patients with solid organ injury a solid decision? J Trauma Acute Care Surg. 2019 Nov;87(5): 1104-12.

56. Gaitanidis A, Breen KA, Nederpelt C, Parks J, Saillant N, Kaafarani HMA, Velmahos GC, Mendoza AE. Timing of thromboprophylaxis in patients with blunt abdominal solid organ injuries undergoing nonoperative management. J Trauma Acute Care Surg. 2021 Jan 1;90(1):148-56.

57. Byrne JP, Mason SA, Gomez D, Hoeft C, Subacius H, Xiong W, Neal M, Pirouzmand F, Nathens AB. Timing of Pharmacologic Venous Thromboembolism Prophylaxis in Severe Traumatic Brain Injury: A Propensity-Matched Cohort Study. J Am Coll Surg. 2016 Oct;223(4):621-631.e5.

58. Brandi G, Schmidlin A, Klinzing S, Schüpbach R, Unseld S, Pagnamenta A. Delayed prophylaxis with unfractionated heparin increases the risk of venous thromboembolic events in patients with moderate to severe traumatic brain injury: a retrospective analysis. Anaesthesiol Intensive Ther. 2020;52(1):28-33.

59. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5; 335(10):701-7.

60. Ginzburg E, Cohn SM, Lopez J, Jackowski J, Brown M, Hameed SM; Miami Deep Vein Thrombosis Study Group. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. Br J Surg. 2003 Nov; 90(11):1338-44.

61. Arabi YM, Al-Hameed F, Burns KEA, Mehta S, Alsolamy SJ, Alshahrani MS, Mandourah Y, Almekhlafi GA, Almaani M, Al Bshabshe A, Finfer S, Arshad Z, Khalid I, Mehta Y, Gaur A, Hawa H, Buscher H, Lababidi H, Al Aithan A, Abdukahil SAI, Jose J, Afesh LY, Al-Dawood A; Saudi Critical Care Trials Group. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. N Engl J Med. 2019 Apr 4; 380(14):1305-15.

62. Hachem LD, Mansouri A, Scales DC, Geerts W, Pirouzmand F. Anticoagulant prophylaxis against venous thromboembolism following severe traumatic brain injury: A prospective observational study and systematic review of the literature. Clin Neurol Neurosurg. 2018 Dec;175:68-73.

63. Denson K, Morgan D, Cunningham R, Nigliazzo A, Brackett D, Lane M, Smith B, Albrecht R. Incidence of venous thromboembolism in patients with traumatic brain injury. Am J Surg. 2007 Mar;193(3):380-3, discussion :383-4.

64. Skrifvars MB, Bailey M, Presneill J, French C, Nichol A, Little L, Duranteau J, Huet O, Haddad S, Arabi Y, McArthur C, Cooper DJ, Bellomo R; EPO-TBI investigators and the ANZICS Clinical Trials Group. Venous thromboembolic events in critically ill traumatic brain injury patients. Intensive Care Med. 2017 Mar;43(3):419-28.

65. Levy AS, Salottolo K, Bar-Or R, Offner P, Mains C, Sullivan M, Bar-Or D. Pharmacologic thromboprophylaxis is a risk factor for hemorrhage progression in a subset of patients with traumatic brain injury. J Trauma. 2010 Apr;68(4): 886-94.

66. Norwood SH, Berne JD, Rowe SA, Villarreal DH, Ledlie JT. Early venous thromboembolism prophylaxis with enoxaparin in patients with blunt traumatic brain injury. J Trauma. 2008 Nov;65(5):1021-6, discussion :1026-7.

67. Mesa Galan LA, Egea-Guerrero JJ, Quintana Diaz M, Vilches-Arenas A. The effectiveness and safety of pharmacological prophylaxis against venous thromboembolism in patients with moderate to severe traumatic brain injury: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2016 Sep;81(3): 567-74.

68. Frisoli FA, Shinseki M, Nwabuobi L, Zeng XL, Adrados M, Kanter C, Frangos SG, Huang PP. Early Venous Thromboembolism Chemoprophylaxis After Traumatic Intracranial Hemorrhage. Neurosurgery. 2017 Dec 1;81(6):1016-20.

69. Margolick J, Dandurand C, Duncan K, Chen W, Evans DC, Sekhon MS, Garraway N, Griesdale DEG, Gooderham P, Hameed SM. A Systematic Review of the Risks and Benefits of Venous Thromboembolism Prophylaxis in Traumatic Brain Injury. Can J Neurol Sci. 2018 Jul;45(4):432-44.

70. Störmann P, Osinloye W, Freiman TM, Seifert V, Marzi I, Lustenberger T. Early Chemical Thromboprophylaxis Does not Increase the Risk of Intracranial Hematoma Progression in Patients with Isolated Severe Traumatic Brain Injury. World J Surg. 2019 Nov;43(11):2804-11.

71. Rivas L, Vella M, Ju T, Fernandez-Moure JS, Sparks A, Seamon MJ, Sarani B. Early Chemoprophylaxis Against Venous Thromboembolism in Patients With Traumatic Brain Injury. Am Surg. 2021 Jan 27:3134820983171.

72. Lu VM, Alvi MA, Rovin RA, Kasper EM. Clinical outcomes following early versus late pharmacologic thromboprophylaxis in patients with traumatic intracranial hemorrhage: a systematic review and meta-analysis. Neurosurg Rev. 2020 Jun; 43(3):861-72.

73. Spano PJ 2nd, Shaikh S, Boneva D, Hai S, McKenney M, Elkbuli A. Anticoagulant chemoprophylaxis in patients with traumatic brain injuries: A systematic review. J Trauma Acute Care Surg. 2020 Mar;88(3):454-60.

74. Phelan HA, Wolf SE, Norwood SH, Aldy K, Brakenridge SC, Eastman AL, Madden CJ, Nakonezny PA, Yang L, Chason DP, Arbique GM, Berne J, Minei JP. A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study. J Trauma Acute Care Surg. 2012 Dec;73(6): 1434-41.

75. Nyquist P, Bautista C, Jichici D, Burns J, Chhangani S, DeFilippis M, Goldenberg FD, Kim K, Liu-DeRyke X, Mack W, Meyer K. Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence-Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society. Neurocrit Care. 2016 Feb;24(1):47-60.

76. Dengler BA, Mendez-Gomez P, Chavez A, Avila L, Michalek J, Hernandez B, Grandhi R, Seifi A. Safety of Chemical DVT Prophylaxis in Severe Traumatic Brain Injury with Invasive Monitoring Devices. Neurocrit Care. 2016 Oct;25(2): 215-23.

77. Cimbanassi S, Chiara O, Leppaniemi A, Henry S, Scalea TM, Shanmuganathan K, Biffl W, Catena F, Ansaloni L, Tugnoli G, De Blasio E, Chieregato A, Gordini G, Ribaldi S, Castriconi M, Festa P, Coccolini F, di Saverio S, Galfano A, Massi M, Celano M, Mutignani M, Rausei S, Pantalone D, Rampoldi A, Fattori L, Miniello S, Sgardello S, Bindi F, Renzi F, Sammartano F. Nonoperative management of abdominal solid-organ injuries following blunt trauma in adults: Results from an International Consensus Conference. J Trauma Acute Care Surg. 2018 Mar;84(3): 517-31.

78. Louis SG, Sato M, Geraci T, Anderson R, Cho SD, Van PY, Barton JS, Riha GM, Underwood S, Differding J, Watters JM, Schreiber MA. Correlation of missed doses of enoxaparin with increased incidence of deep vein thrombosis in trauma and general surgery patients. JAMA Surg. 2014 Apr;149(4):365-70.

79. Salottolo K, Offner P, Levy AS, Mains CW, Slone DS, Bar-Or D. Interrupted pharmocologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. J Trauma. 2011 Jan;70(1):19-24, discussion :25-6.

80. Booth K, Rivet J, Flici R, Harvey E, Hamill M, Hundley D, Holland K, Hubbard S, Trivedi A, Collier B. Progressive Mobility Protocol Reduces Venous Thromboembolism Rate in Trauma Intensive Care Patients: A Quality Improvement Project. J Trauma Nurs. 2016 Sep-Oct;23(5):284-9.

81. Regner JL, Shaver CN; SWSC Multicenter Trials Group. Determining the impact of culture on venous thromboembolism prevention in trauma patients: A Southwestern Surgical Congress Multicenter trial. Am J Surg. 2019 Jun;217(6): 1030-6.

82. MacCallum KP, Kalata S, Darcy D, Parsikia A, Chao E, Stone ME, Teperman S, Reddy SH. Prolonged use of spinal precautions is associated with increased morbidity in the trauma patient. Injury. 2020 Feb;51(2):317-21.

83. Haac BE, Van Besien R, O'Hara NN, Slobogean GP, Manson TT, O'Toole RV, Johal H, Berger PZ, Reahl GB, Marinos D, Degani Y, Mascarenhas D, Connelly D, Scalea TM, Stein DM. Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin. J Trauma Acute Care Surg. 2018 Apr; 84(4):564-74.

84. O'Toole RV, Stein DM, Frey KP, O'Hara NN, Scharfstein DO, Slobogean GP, Taylor TJ, Haac BE, Carlini AR, Manson TT, Sudini K, Mullins CD, Wegener ST, Firoozabadi R, Haut ER, Bosse MJ, Seymour RB, Holden MB, Gitajn IL, Goldhaber SZ, Eastman AL, Jurkovich GJ, Vallier HA, Gary JL, Kleweno CP, Cuschieri J, Marvel D, Castillo RC; METRC. PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): a randomised pragmatic trial protocol comparing aspirin versus low-molecular-weight heparin for blood clot prevention in orthopaedic trauma patients. BMJ Open. 2021 Mar 24;11(3):e041845.

85. Haut ER, Lau BD, Kraenzlin FS, Hobson DB, Kraus PS, Carolan HT, Haider AH, Holzmueller CG, Efron DT, Pronovost PJ, Streiff MB. Improved prophylaxis and decreased rates of preventable harm with the use of a mandatory computerized clinical decision support tool for prophylaxis for venous thromboembolism in trauma. Arch Surg. 2012 Oct;147(10):901-7.

86. Machado-Aranda DA, Jakubus JL, Wahl WL, Cherry-Bukowiec JR, To KB, Park PK, Raghavendran K, Napolitano LM, Hemmila MR. Reduction in Venous Thromboembolism Events: Trauma Performance Improvement and Loop Closure Through Participation in a State-Wide Quality Collaborative. J Am Coll Surg. 2015 Sep;221(3):661-8.

3 - What is the best way to determine acute blood loss and predict operative blood loss in trauma patients with orthopaedic injuries?

Response/Recommendation: Multiple factors have been studied to assess blood loss in acute trauma patients, and to predict the need for transfusion. Adequate risk stratification involves consideration of the patient's vital signs, laboratory data, injuries, and medical history.

Strength of Recommendation: Low.

Delegates vote: Agree 88.37% Disagree 4.65% Abstain 6.98% (Strong Consensus).

Rationale: Bleeding is a significant source of morbidity and mortality in trauma patients[87,88]. Adequate resuscitation is an important aspect of management of trauma patients[89-91]. In patients requiring surgery, under-resuscitation may delay operative treatment, and is associated with increased risk of complications. Many factors indicate an increased risk of substantial bleeding in trauma patients. A patient's presenting vital signs, temperature, coagulopathic state, severity of injuries, mechanism of injury, as well as their medical comorbidities all contribute to the risk of bleeding in acute trauma. Prehospital care may also have an effect. A variety of scoring systems have been developed to guide clinicians in evaluating this risk[90,92-99].

Clinicians routinely use a trauma patient's presenting blood pressure and tachycardia to evaluate sustained blood loss[88,94,100]. Shock index, defined as heart rate/systolic blood pressure (HR/SBP), is a validated tool in stratifying blood loss and is simple to calculate in the acute trauma setting. El-Menyar et al., found that shock index greater than 0.8 was an independent predictor of transfusion and mortality[94]. Similarly, Vandromme et al., showed increased transfusion rates in patients with shock index greater than 0.9, and five-fold increase in transfusion rates with shock index greater than 1.1[100]. Cannon et al., found higher mortality in patients with a presenting shock index greater than 0.9[96].

Other scoring systems for prior acute blood loss have been developed that supplement vital signs data with additional presenting laboratory values. The assessment of blood consumption (ABC) score considers SBP < 90, HR > 120, penetrating mechanism, and a positive Febuxostat versus Allopurinol streamlined trial (FAST) study[92,95]. Patients with at least two of these are likely to require massive transfusion. However, Schroll et al., found ABC score to have lower sensitivity but greater specificity than shock index for predicting massive transfusion[101]. Further systems include the bleeding audit for trauma & triage (BATT) score, developed to predict hemorrhagic death in trauma, which uses SBP < 100, BP > 100, as well as respiratory rate, the Glasgow coma scale (GCS) score, age, penetrating mechanism, and high velocity trauma[98]. The head injury severity score (HISS) uses presenting labs of glucose, lactate, pH, potassium, and pO_2 to predict mortality and intensive care unit (ICU) stay[97].

In addition to a patient's presenting laboratory values and vital signs, overall injury burden and mechanism of injury contribute to bleeding risk. Rainer et al., showed that patients with displaced pelvic fractures had odds ratio of 7.6 for requiring massive transfusion[102]. Additionally, they showed that positive FAST score, injury severity score (ISS) greater than 25, and high energy motor vehicle collision (MVC) were associated with transfusion[102]. Further, the physiologic response to trauma varies by mechanism and has a significant impact on bleeding risk[103]. Blunt trauma without shock promotes a prothrombotic response due to diffuse tissue damage[104]. However, penetrating trauma or trauma with shock may have produced a coagulopathic response associated with increased bleeding risk[104]. Given the variable effects of trauma on coagulation pathways, viscoelastic assays have been studied to monitor hemostasis in acute trauma[88,103]. The use of thromboelastography (TEG) is used more widely in Europe than in North America, but more locations are evaluating this methodology[105].

Patients requiring surgery are at increased risk of bleeding, and this varies with type of surgery needed. Patients who required hemostatic or endovascular surgery have been shown to require massive transfusion more frequently[106]. In femur fracture patients receiving intramedullary nails, perioperative blood loss has been

estimated at about 1,200cc using dilutional methods[107]. In acetabular fracture fixation, reported blood loss can be more than 2,000 cc depending on the pattern and approach, with approximately 40% requiring transfusion[108-110].

Medical history must also be considered when evaluating bleeding risk in trauma patients. Taking a personal and family history of bleeding is recommended in all preoperative patients[111]. Medication history should routinely be reviewed, as patients on anticoagulation are also at higher risk of bleeding after trauma. Williams et al report anticoagulation and international normalized ratio (INR) > 1.5 were independent risk factors for mortality in trauma patients[91].

Appropriate risk stratification for bleeding in trauma patients requires a multi-factorial approach. Multiple scoring systems exist to evaluate vital signs and laboratory data. In particular, hypotension and tachycardia on presentation consistently prove to be important factors in predicting significant blood loss. In addition to these tools, physicians should also consider overall injury burden, mechanism of injury, and patient medical history to appropriately stratify bleeding risk.

Factors that influence blood loss in orthopaedic trauma patients:

Injury related factors

1. Presenting vitals/labs
    1. Shock index - (HR/SBP > 0.8) an independent predictor of transfusion and mortality[94].
    2. HISS score uses presenting labs of glucose, lactate, pH, potassium, pO2 to predict mortality and ICU stay[97].
2. Overall injury burden/injury severity score
    1. Displaced pelvic fracture, positive FAST, increased ISS → increased risk of needing massive transfusion[102].
    2. BATT score to predict hemorrhagic death: age, GCS, mechanism of injury, vital signs[98]. The prediction of acute coagulopathy of trauma (PACT) score used similar variables[93].
3. Mechanism of injury
    1. Blunt trauma with shock associated with increased risk of bleeding. The trauma brain injury (TBI) severity score is also associated with delayed clot formation[104].
    2. Higher energy injury such as MVC associated with greater risk of massive transfusion[106].
    3. Can consider viscoelastic assays, however not widely used at this time
    4. Planned surgery
        1. Major surgery associated with > 2% blood loss (joint replacement, major orthopaedic surgery, operation > 45 mins). Lower risk with arthroscopy, hand, or foot surgeries[112].
        2. Patients who required hemostatic or endovascular surgery more likely to need massive transfusion[106].

Patient-related factors

1. Bleeding related comorbidities
    1. Medical and family history of bleeding should be obtained in all preoperative patients[111].
    2. Medications - anticoagulants, antiplatelet agents
        1. Anticoagulation and INR > 1.5 independent risk factors for bleeding and mortality[91].
    3. Additional medical comorbidities (capacity to compensate for blood loss/increased risk)
        1. BATT score shows correlation between increased age and hemorrhagic death[98].

Justin E. Kleiner, Paul Tornetta III

References

87. Maegele M. Acute traumatic coagulopathy: Incidence, risk stratification and therapeutic options. World J Emerg Med. 2010;1(1):12-21.

88. Maegele M. The European Perspective on the Management of Acute Major Hemorrhage and Coagulopathy after Trauma: Summary of the 2019 Updated European Guideline. J Clin Med. 2021 Jan 19;10(2):362.

89. Tran A, Matar M, Lampron J, Steyerberg E, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2018 Mar;84(3):505-16.

90. Cornero SG, Maegele M, Lefering R, Abbati C, Gupta S, Sammartano F, Cimbanassi S, Chiara O. Predictive Factors for Massive Transfusion in Trauma: A Novel Clinical Score from an Italian Trauma Center and German Trauma Registry. J Clin Med. 2020 Oct 10;9(10):3235.

91. Williams TM, Sadjadi J, Harken AH, Victorino GP. The necessity to assess anticoagulation status in elderly injured patients. J Trauma. 2008 Oct;65(4):772-6, discussion :776-7.

92. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma. 2009 Feb;66(2):346-52.

93. Peltan ID, Rowhani-Rahbar A, Vande Vusse LK, Caldwell E, Rea TD, Maier RV, Watkins TR. Development and validation of a prehospital prediction model for acute traumatic coagulopathy. Crit Care. 2016 Nov 16;20(1):371.

94. El-Menyar A, Goyal P, Tilley E, Latifi R. The clinical utility of shock index to predict the need for blood transfusion and outcomes in trauma. J Surg Res. 2018 Jul;227:52-9.

95. Cantle PM, Cotton BA. Prediction of Massive Transfusion in Trauma. Crit Care Clin. 2017 Jan;33(1):71-84.

96. Cannon CM, Braxton CC, Kling-Smith M, Mahnken JD, Carlton E, Moncure M. Utility of the shock index in predicting mortality in traumatically injured patients. J Trauma. 2009 Dec;67(6):1426-30.

97. Bhat A, Podstawczyk D, Walther BK, Aggas JR, Machado-Aranda D, Ward KR, Guiseppi-Elie A. Toward a hemorrhagic trauma severity score: fusing five physiological biomarkers. J Transl Med. 2020 Sep 14;18(1):348.

98. Ageron FX, Coats TJ, Darioli V, Roberts I. Validation of the BATT score for prehospital risk stratification of traumatic haemorrhagic death: usefulness for tranexamic acid treatment criteria. Scand J Trauma Resusc Emerg Med. 2021 Jan 6;29(1):6.

99. Yücel N, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, Neugebauer EA, Wappler F, Bouillon B, Rixen D; Polytrauma Study Group of the German Trauma Society. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma. 2006 Jun;60(6):1228-36, discussion :1236-7.

100. Vandromme MJ, Griffin RL, Kerby JD, McGwin G Jr, Rue LW 3rd, Weinberg JA. Identifying risk for massive transfusion in the relatively normotensive patient: utility of the prehospital shock index. J Trauma. 2011 Feb;70(2):384-8, discussion :388-90.

101. Schroll R, Swift D, Tatum D, Couch S, Heaney JB, Llado-Farrulla M, Zucker S, Gill F, Brown G, Buffin N, Duchesne J. Accuracy of shock index versus ABC score to predict need for massive transfusion in trauma patients. Injury. 2018 Jan;49(1):15-9.

102. Rainer TH, Ho AMH, Yeung JHH, Cheung NK, Wong RS, Tang N, Ng SK, Wong GK, Lai PB, Graham CA. Early risk stratification of patients with major trauma requiring massive blood transfusion. Resuscitation. 2011 Jun;82(6):724-9.

103. Maegele M, Spinella PC, Schöchl H. The acute coagulopathy of trauma: mechanisms and tools for risk stratification. Shock. 2012 Nov;38(5):450-8.
104. Duque P, Mora L, Levy JH, Schöchl H. Pathophysiological response to trauma-induced coagulopathy: A comprehensive review. Anesth Analg. 2020 Mar;130(3): 654-64.
105. George MJ, Aroom KR, Wade CE, Cox CS Jr, Gill BS. A Novel Platelet Function Assay for Trauma. J Surg Res. 2020 Feb;246:605-13.
106. Charbit J, Lakhal K, Deras P, Dehon A, Latry P, Boissier E, Schved JF, Capdevila X. Influence of surgical bleeding on the relationship between admission coagulopathy and risk of massive transfusion: lesson from 704 severe trauma patients. Vox Sang. 2016 Aug;111(2):151-60.
107. Lieurance R, Benjamin JB, Rappaport WD. Blood loss and transfusion in patients with isolated femur fractures. J Orthop Trauma. 1992;6(2): 175-9.
108. Lack WD, Crist BD, Seymour RB, Harvin W, Karunakar MA; TXA Study Group‖. Effect of Tranexamic Acid on Transfusion: A Randomized Clinical Trial in Acetabular Fracture Surgery. J Orthop Trauma. 2017 Oct;31(10):526-30.
109. Bigsby E, Acharya MR, Ward AJ, Chesser TJS. The use of blood cell salvage in acetabular fracture internal fixation surgery. J Orthop Trauma. 2013 Oct;27(10): e230-3.
110. Wadhwa H, Chen MJ, Tigchelaar SS, Bellino MJ, Bishop JA, Gardner MJ. Hypotensive Anesthesia does not reduce Transfusion Rates during and after Acetabular Fracture Surgery. Injury. 2021 Jul;52(7):1783-7.
111. Chee YL, Crawford JC, Watson HG, Greaves M; British Committee for Standards in Haematology. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. Br J Haematol. 2008 Mar;140(5): 496-504.
112. Spyropoulos AC, Brohi K, Caprini J, Samama CM, Siegal D, Tafur A, Verhamme P, Douketis JD; SSC Subcommittee on Perioperative and Critical Care Thrombosis and Haemostasis of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee Communication: Guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: Recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. J Thromb Haemost. 2019 Nov;17(11): 1966-72.

4 - What is the optimal management of patients on antiplatelet and/or anticoagulation presenting with acute lower extremity trauma and needing surgery?

Response/Recommendation: The optimal management of patients on antiplatelets and/or anticoagulants presenting with acute lower extremity trauma and needing surgery should involve a risk-benefit assessment weighing the risk of bleeding against the risk of thrombosis. Depending on the degree of urgency, extent of trauma and patient's coagulation status, the optimal approach may involve postponing the procedure and monitoring the coagulation status, perioperative bridging therapy, or acute reversal of anticoagulation.

Most studies recommend that patients receiving aspirin (ASA) can undergo surgery safely without delay. In patients taking oral anticoagulants, coagulation tests should be performed. If surgery cannot be delayed, anticoagulant reversal agents should be administered. Recent literature has suggested that the use of reversal agents does not lead to adverse outcomes following lower extremity trauma surgery. In addition, early surgical treatment of hip fractures despite anticoagulation may be prudent in a subgroup of patients.

Strength of Recommendation: Limited.

Delegates vote: Agree 90.91% Disagree 6.82% Abstain 2.27% (Strong Consensus).

Rationale: Antithrombotic agents can be broadly subdivided into two classes: anticoagulants and antiplatelet medications[113,114]. When patients on these agents undergo orthopaedic procedures, management should entail an individualized assessment of the risk of bleeding as well as the risk of thrombosis. Approximately 1 in 10 surgical patients are prescribed chronic anticoagulation or antiplatelet therapy, and majority will require temporary antithrombotic interruption, bridging or reversal[113,115-117]. It is widely established that urgent, non-deferrable surgery should not be delayed in patients on antiplatelets, even in those receiving dual antiplatelet therapy[118,119]. In contrast, given the wide variety of anticoagulation agents available[120], there is substantial heterogeneity with regards to the perioperative management of these patients. Not surprisingly, there is still a lack of consensus on this topic within the orthopaedic community[121].

The majority of recommendations regarding the interruption of anticoagulant or antiplatelet therapy in trauma patients with a moderate to high risk of bleeding are reflected in the latest clinical guidelines of various professional societies[118,122,123]. These strategies have largely been developed from general surgical and neurosurgical literature[124]. As existing guidelines are based on expert opinion, consensus, and retrospective studies, the level of evidence is extremely limited. In addition, most recommendations have been restricted to the safety of neuraxial anesthesia rather than trauma surgery *per se*[118,122,125].

Recent data has shown that hip fracture patients are prone to prolonged elimination half-lives of direct oral anticoagulants (DOAC), with almost 50% of patients still having therapeutic levels at the time of surgery[126]. Patients on DOAC have increased delays to surgery compared to patients who are not on anticoagulation or those on vitamin K antagonists. Average time to surgery for DOAC patients may range from 35.0 hours to 66.9 hours[127,128]. King et al.[129], concluded that taking DOAC on admission was not a reason to delay hip fracture surgery. Similarly, Bruckbauer et al.[130], suggested that early hip fracture surgery should be indicated in DOAC patients. Consistent with these findings, Schuetze et al.[131], noted that early surgical care of proximal femur fractures was safe in patients on anticoagulants, as long as preparations for possible intraoperative transfusions were made. In contrast, Gosch et al.[132], found that hip fracture patients on oral anticoagulation had higher rates of in-hospital mortality, transfusion (requiring 3 or more packed red cells), major bleeding, hemoglobin drop of 6 g/dL or more, myocardial infarction, stroke, and thromboembolic events, compared to controls who were not on anticoagulation.

Besides hip fractures, data on the management of other lower extremity fractures in patients on antiplatelet or anticoagulation remains scarce. Recent literature has demonstrated a trend away from the routine use of bridging anticoagulation[133], with several reports suggesting that the administration of reversal agents may not lead to adverse outcomes in lower extremity trauma surgery[134]. Ultimately, the risks associated with delaying operative care in lower extremity trauma is fracture- and patient-specific. Depending on the degree of urgency, extent of trauma and patient's coagulation status, the optimal approach may

involve postponing the procedure and monitoring the coagulation status, perioperative bridging therapy, or acute reversal of anticoagulation.

The following recommendations are brief excerpts from current guidelines and recent literature, which provide an update on the most common antithrombotic reversal strategies or corrective measures. These strategies should be carried out in collaboration with cardiology, anesthesiology, and other specialties.

Warfarin: There is an ongoing debate regarding the perioperative management of trauma patients on warfarin. Some authors advocate a watch-and-wait approach, while others recommend urgent reversal. It is well established that fracture surgery can be expedited by reversing the anticoagulation effect of warfarin with vitamin K[135,136]. The National Institute for Health and Care Excellence (NICE) guidelines have underscored the importance of prompt surgical management of elderly patients with hip fractures within the first 36 hours, reiterating that delays related to anticoagulation are often unjustified[137]. Gulati et al.[138], and Moores et al.[139], advised that the action of warfarin should be reversed in order to expedite hip fracture surgery. This reversal can be achieved with vitamin K, prothrombin complex concentrate ([PCC] Beriplex), fresh frozen plasma (FFP), or recombinant factor VIIa[116,140].

For surgeons adopting a watch-and-wait approach, the 2017 American College of Cardiology (ACC) guidelines recommended checking the international normalized ratio (INR) 5 to 7 days before surgery. The INR should then be rechecked within 24 hours of surgery to ensure normalization. Bridging anticoagulation, typically with low-molecular-weight heparin (LMWH), is undertaken in patients at high thrombotic risk, which has been defined as patients with a Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke or transitory ischemic attack (TIA) or thromboembolism - Vascular disease, Age 65 – 74 years, female Sex category (CHA_2DS_2-VASc) score of ≥ 7 (greater than 10% annual risk of stroke or embolism) or patients with a thrombotic event within the past 3 months[114].

Dabigatran: For procedures with high bleeding risk, ACC guidelines recommend an antithrombotic interruption (ATI) period of 2 days before surgery without the need for bridging anticoagulation. In patients with impaired renal function (creatinine clearance < 50 mL/min), a longer ATI duration of 4 days is recommended[114]. The fourth edition of the American Society of Regional Anesthesia (ASRA) guidelines suggest only a 34-hour ATI interval before neuraxial block, and 72 to 90 hours in patients with renal impairment[141].

In the event of overdose, its effect can be reversed with hemodialysis and antidote administration using idarucizumab (Praxbind)[142]. The approved dose is two 2.5 g IV bolus infusions administered within 15 min[113]. In life-threatening bleeding, this can be combined with tranexamic acid (TXA) (1 g. IV). PCC is another option, although there is limited evidence regarding its use in patients on DOAC. The use of FFP is currently restricted to rescue therapy if other alternatives are not available[125,143].

Low-molecular-weight heparin (LMWH): For patients on treatment doses of LMWH, surgery under neuraxial anesthesia should be delayed for at least 24 hours. For patients on prophylactic doses of LMWH, this delay can be reduced to 12 hours[122].

Oral anticoagulants should be discontinued prior to procedures with a moderate to high risk of bleeding including long bone fractures and hip fractures[118]. In patients with a low to moderate thrombotic risk, perioperative bridging therapy may not be necessary. However, for patients with a high thromboembolic risk, bridging therapy with LMWH at prophylactic doses can be administered. If urgent surgery is indicated, the use of reversal agents should be considered[118,143].

Rivaroxaban: The ACC guidelines recommend a discontinuation period of 2 days before high-risk procedures, with a longer ATI period of 3 days in the setting of renal impairment. The ASRA guidelines recommend discontinuing rivaroxaban 22 to 26 hours before neuraxial block except in the setting of renal impairment, in which case 44 to 65 hours is recommended[141].

Rivaroxaban is not removed by hemodialysis. Andexanet alfa (AndexXa) is the first and only antidote for patients taking rivaroxaban (Xarelto), apixaban (Eliquis) or edoxaban (Savaysa)[144]. Activated charcoal may help to reduce absorption in cases of acute over-ingestion of DOAC and should be administered within 1 - 2 hours of novel oral anticoagulants (NOAC) intake[145].

Apixaban: The ACC recommends an ATI period of 2 days. As 27% of the drug is renally cleared, a longer ATI of 3 days is recommended in the setting of renal impairment[2]. The ASRA guidelines recommend discontinuing apixaban 26 to 30 hours before neuraxial procedures, and 40 to 75 hours in patients with a serum creatinine of 1.5 mg/dL or more[141].

Edoxaban: No published studies have investigated the periprocedural safety of continued use of edoxaban, nor the appropriate ATI period for this anticoagulant in the setting of orthopaedic surgery. The ACC recommends an ATI period of 48 hours before surgery in patients with normal renal function and 72 hours in patients with renal impairment[114]. The ASRA guidelines recommend a 20- to 28-hour interruption period before neuraxial procedures, and 40 to 70 hours for patients with renal impairment[141].

Acetyl salicylic acid – Aspirin (ASA): Bleeding risk while taking ASA in the perioperative period has been extensively studied, but conflicting results have been reported[116,117]. In particular, several studies have demonstrated the safety of continuing ASA during elective hip and knee surgery[116,117].

Recent guidelines recommend continuing ASA in patients at moderate to high risk of cardiovascular events and discontinuing ASA 7 to 10 days before surgery in patients at low risk

of cardiovascular events, acknowledging that the discontinuation of ASA may carry an increased risk of thrombotic events in patients with strong cardiovascular risk factors[117,146].

Surgery should not be postponed in patients receiving ASA as the low risk of bleeding does not justify the surgical delay[119,147,148]. The ASRA guidelines also recommend continuing ASA regardless of dosage or indication before neuraxial procedures, citing multiple studies demonstrating that ASA does not significantly increase the risk of spinal hematomas following neuraxial blocks[141]. Notwithstanding, there is a risk of bleeding if ASA is taken in combination with other thromboprophylactic medication, hence ASA may be withheld during inpatient stay unless indicated for unstable angina or recent/frequent transient ischemic attacks[135].

Clopidogrel: The 2012 American College of Chest Physicians (ACCP) guidelines recommend stopping clopidogrel or prasugrel 5 days before surgery[146]. Similarly, the ASRA guidelines recommend discontinuing clopidogrel 5 days before neuraxial procedures. The recent Scottish Intercollegiate Guidelines Network (SIGN) recommend that surgery should not be delayed, and platelets should not be administered prophylactically, although marginally greater blood loss should be anticipated. This is also associated with an increased risk of spinal hematoma when regional anesthesia is employed[135]. Bridging is not required during temporary clopidogrel discontinuation in the perioperative setting, but ASA should be continued in patients on dual antiplatelet therapy (DAPT) after stent placement[149].

The antiplatelet effect of clopidogrel can only be overcome with platelet transfusions, since clopidogrel irreversibly inhibits platelet function and there is no known antidote for this drug. Platelet concentrates may be administered if platelet dysfunction is documented in a patient who requires urgent surgery, suffers continued bleeding, or sustains an intracranial hemorrhage. Desmopressin (0.3 μg/kg) may also be administered in such patients[123].

Prasugrel: No data on the safety of continuing prasugrel in the setting of orthopaedic surgery has been published. The AACP recommends stopping clopidogrel or prasugrel 5 days before cardiac surgery[146], whereas the ASRA recommends discontinuing prasugrel 7 days before neuraxial block[141]. No available reversal agent for prasugrel exists.

Ticagrelor: No data exists regarding the continuation of ticagrelor in orthopaedic procedures. Platelet aggregation returns to normal within 5 days of discontinuation of ticagrelor[150]. Consequently, the ASRA guidelines recommend discontinuing ticagrelor 5 days before any procedure[141].

No specific reversal agent exists. PB2452, a monoclonal antibody fragment that binds ticagrelor, is being developed as an antidote for patients requiring urgent surgery or experiencing life-threatening bleeding[151,152].

Conclusion: Given the varying indications for antithrombotics, medication diversity and patient heterogeneity, defining the optimal strategy for patients on these medications who present with acute lower extremity trauma and require urgent surgery remains a challenging task. Periprocedural interruption and/or correction of anticoagulant therapy is often a complex risk-benefit intervention, requiring a thorough assessment of the patient's bleeding and thrombotic risks. The need to reverse the effect of the anticoagulant or antiplatelet drug should be determined by the need to perform surgery urgently. If surgery cannot be delayed, reversal agents or other corrective measures should be administered. Ultimately, orthopaedic surgeons should always strive to manage these patients in collaboration with their colleagues in cardiology, anesthesia, and other medical specialties.

Dragan K. Radoičić, Francisco Chana-Rodríguez, Antonio Benjumea-Carrasco, Jesús Gómez-Vallejo

References

113. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. N Engl J Med. 2013 May 30;368(22):2113-24.

114. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, Spinler SA. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017 Feb 21;69(7):871-98.

115. American Heart Association. www.heart.org. Accessed December 2, 2021. https://www.heart.org/en/

116. Barlow BT, Hannon MT, Waldron JE. Preoperative Management of Antithrombotics in Arthroplasty. J Am Acad Orthop Surg. 2019 Dec 1;27(23):878-86.

117. Hornor MA, Duane TM, Ehlers AP, Jensen EH, Brown PS Jr, Pohl D, da Costa PM, Ko CY, Laronga C. American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication. J Am Coll Surg. 2018 Nov;227(5):521-536.e1.

118. Vivas D, Roldán I, Ferrandis R, Marín F, Roldán V, Tello-Montoliu A, Ruiz-Nodar JM, Gómez-Doblas JJ, Martín A, Llau JV, Ramos-Gallo MJ, Muñoz R, Arcelus JI, Leyva F, Alberca F, Oliva R, Gómez AM, Montero C, Arikan F, Ley L, Santos-Bueso E, Figuero E, Bujaldón A, Urbano J, Otero R, Hermida JF, Egocheaga I, Llisterri JL, Lobos JM, Serrano A, Madridano O, Ferreiro JL; Expert reviewers. Perioperative and Periprocedural Management of Antithrombotic Therapy: Consensus Document of SEC, SEDAR, SEACV, SECTCV, AEC, SECPRE, SEPD, SEGO, SEHH, SETH, SEMERGEN, SEMFYC, SEMG, SEMICYUC, SEMI, SEMES, SEPAR, SENEC, SEO, SEPA, SERVEI, SECOT and AEU. Rev Esp Cardiol (Engl Ed). 2018 Jul;71(7):553-64.

119. Columbo JA, Lambour AJ, Sundling RA, Chauhan NB, Bessen SY, Linshaw DL, Kang R, Riblet NBV, Goodney PP, Stone DH. A Meta-analysis of the Impact of Aspirin, Clopidogrel, and Dual Antiplatelet Therapy on Bleeding Complications in Noncardiac Surgery. Ann Surg. 2018 Jan;267(1):1-10.

120. Riedel MD, Watkins IT, McCormick JR, Van Lancker HP. Anticoagulation Strategies for the Orthopaedic Surgeon: Reversal and Timelines. Arch Bone Jt Surg. 2020 May;8(3):457-60.

121. Pean CA, Goch A, Christiano A, Konda S, Egol K. Current Practices Regarding Perioperative Management of Patients With Fracture on Antiplatelet Therapy: A Survey of Orthopedic Surgeons. Geriatr Orthop Surg Rehabil. 2015 Dec;6(4):289-94.

122. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol. 2017 Jun;34(6):332-95.

123. Spahn DR, Bouillon B, Cerny V, et al The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23(1):98. doi:10.1186/s13054-019-2347-3

124. Yassa R, Khalfaoui MY, Hujazi I, Sevenoaks H, Dunkow P. Management of anticoagulation in hip fractures: A pragmatic approach. EFORT Open Rev. 2017 Sep 21;2(9):394-402.

125. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, Torp-Pedersen C, Kjeldsen K, Lewis BS, Drexel H, Kaski JC, Atar D, Storey RF, Lip GYH, Verheugt FWA, Agewall S. Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and

recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2017 Jun 7;38(22):1710-6.

126. Viktil KK, Lehre I, Ranhoff AH, Molden E. Serum Concentrations and Elimination Rates of Direct-Acting Oral Anticoagulants (DOACs) in Older Hip Fracture Patients Hospitalized for Surgery: A Pilot Study. Drugs Aging. 2019 Jan;36(1):65-71.

127. Frenkel Rutenberg T, Velkes S, Vitenberg M, Leader A, Halavy Y, Raanani P, Yassin M, Spectre G. Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants. Thromb Res. 2018 Jun;166:106-12.

128. Taranu R, Redclift C, Williams P, Diament M, Tate A, Maddox J, Wilson F, Eardley W. Use of Anticoagulants Remains a Significant Threat to Timely Hip Fracture Surgery. Geriatr Orthop Surg Rehabil. 2018 Mar 22;9: 2151459318764150.

129. King K, Polischuk M, Lynch G, Gergis A, Rajesh A, Shelfoon C, Kattar N, Sriselvakumar S, Cooke C. Early Surgical Fixation for Hip Fractures in Patients Taking Direct Oral Anticoagulation: A Retrospective Cohort Study. Geriatr Orthop Surg Rehabil. 2020 Jul 27;11:2151459320944854.

130. Bruckbauer M, Prexl O, Voelckel W, Ziegler B, Grottke O, Maegele M, Schöchl H. Impact of Direct Oral Anticoagulants in Patients With Hip Fractures. J Orthop Trauma. 2019 Jan;33(1):e8-13.

131. Schuetze K, Eickhoff A, Dehner C, Gebhard F, Richter PH. Impact of oral anticoagulation on proximal femur fractures treated within 24h- A retrospective chart review .Injury .2019 Nov ;50(11):2040-4.

132. Gosch M, Jacobs M, Bail H, Grueninger S, Wicklein S. Outcome of older hip fracture patients on anticoagulation: a comparison of vitamin K-antagonists and Factor Xa inhibitors. Arch Orthop Trauma Surg. 2021 Apr;141(4):637-43.

133. Morris JC, O'Connor MI. Anticoagulation Management in Geriatric Orthopedic Trauma Patients. Geriatr Orthop. 2020;9(4):288-95.

134. Yoo MS, Zhu S, Jiang SF, Hammer HL, McBride WJ, McCarthy CM, Green CE, Ananias MP. Association of Reversal of Anticoagulation Preoperatively on 30-Day Mortality and Outcomes for Hip Fracture Surgery. Am J Med. 2020 Aug;133(8): 969-975.e2.

135. Ktistakis I, Giannoudis V, Giannoudis PV. Anticoagulation therapy and proximal femoral fracture treatment: An update. EFORT Open Rev. 2017 Mar 13; 1(8):310-5.

136. Tharmarajah P, Pusey J, Keeling D, Willett K. Efficacy of warfarin reversal in orthopedic trauma surgery patients. J Orthop Trauma. 2007 Jan;21(1):26-30.

137. Recommendations | Hip fracture: management | Guidance | NICE. Accessed December 2, 2021. https://www.nice.org.uk/guidance/cg124/chapter/Recommendations

138. Gulati V, Newman S, Porter KJ, Franco LCS, Wainwright T, Ugoigwe C, Middleton R. Implications of anticoagulant and antiplatelet therapy in patients presenting with hip fractures: a current concepts review. Hip Int. 2018 May;28(3): 227-33.

139. Moores TS, Beaven A, Cattell AE, Baker C, Roberts PJ. Preoperative warfarin reversal for early hip fracture surgery. J Orthop Surg (Hong Kong). 2015 Apr;23(1): 33-6.

140. Wadhera RK, Russell CE, Piazza G. Cardiology patient page. Warfarin versus novel oral anticoagulants: how to choose? Circulation. 2014 Nov 25;130(22): e191-3.

141. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018 Apr;43(3):263-309.

142. Glund S, Stangier J, van Ryn J, Schmohl M, Moschetti V, Haazen W, De Smet M, Gansser D, Norris S, Lang B, Reilly P, Kreuzer J. Effect of Age and Renal Function on Idarucizumab Pharmacokinetics and Idarucizumab-Mediated Reversal of Dabigatran Anticoagulant Activity in a Randomized, Double-Blind, Crossover Phase Ib Study. Clin Pharmacokinet. 2017 Jan;56(1):41-54.

143. Eikelboom JW, Kozek-Langenecker S, Exadaktylos A, Batorova A, Boda Z, Christory F, Gornik I, Kėkštas G, Kher A, Komadina R, Koval O, Mitic G, Novikova T, Pazvanska E, Ratobilska S, Sütt J, Winder A, Zateyshchikov D. Emergency care of patients receiving non-vitamin K antagonist oral anticoagulants. Br J Anaesth. 2018 Apr;120(4):645-56.

144. Kustos SA, Fasinu PS. Direct-Acting Oral Anticoagulants and Their Reversal Agents-An Update. Medicines (Basel). 2019 Oct 15;6(4):E103.

145. Mujer MTP, Rai MP, Atti V, Dimaandal IL, Chan AS, Shrotriya S, Gundabolu K, Dhakal P. An Update on the Reversal of Non-Vitamin K Antagonist Oral Anticoagulants. Adv Hematol. 2020 Jan 27;2020:7636104.

146. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e326S-50S.

147. Keeling D, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. Br J Haematol. 2016 Nov;175(4):602-13.

148. Kennedy MT, Roche S, Fleming SM, Lenehan B, Curtin W. The association between aspirin and blood loss in hip fracture patients. Acta Orthop Belg. 2006 Jan; 72(1):29-33.

149. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. J Nucl Cardiol. 2015 Feb;22(1):162-215.

150. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009 Dec 22;120(25): 2577-85.

151. Bhatt DL, Pollack CV, Weitz JI, Jennings LK, Xu S, Arnold SE, Umstead BR, Mays MC, Lee JS. Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers. N Engl J Med. 2019 May 9;380(19):1825-33.

152. Nylander S, Pehrsson S, Inghardt T, Antonsson T, Svensson P, Sjögren T, Öster L, Janefeldt A, Sandinge AS, Newton P, Keyes F, Austin M, Buchanan A. A specific antidote for ticagrelor. J Am Coll Cardiol. 2015;65(10_Supplement):A253.

5 - Concerning VTE risk, which surgeries can be considered major and which surgeries can be considered non-major in orthopaedic trauma?

Response/Recommendation: Surgical procedures in the upper extremity and distal to the ankle can be considered non-major. The risk of venous thromboembolism (VTE) increases in the lower limb from the distal leg (or ankle) to the pelvis, with higher risk associated with more proximal surgeries. In addition to location of surgery, length of surgery and expected post-operative mobility must be considered.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.56% Disagree 4.44% Abstain 0.00% (Strong Consensus).

Rationale: Venous thromboembolism (VTE) is a significant source of morbidity and mortality following orthopedic surgery[153,154]. The risk of VTE following orthopaedic surgery varies significantly based on many patient and surgical factors[155-159]. It is important to stratify this risk in order to develop an appropriate anticoagulation plan post-operatively[160-162].

Most lower extremity surgery is associated with significant VTE risk and should be considered major in patients with isolated tibia or distal lower leg fracture, meta-analysis showed that low-molecular-weight heparin (LMWH) reduces risk of overall deep venous thrombosis (DVT) (relative risk 0.7)[163]. However, anticoagulation was not shown to reduce rate of clinically important VTE, defined as proximal or symptomatic DVT[163]. In elective arthroplasty patients, symptomatic VTE occurs in 2-3%, and asymptomatic DVT has been reported in up to 40% of patients without anticoagulant thromboprophylaxis[164,165]. Further, the Caprini score was introduced to predict the risk of VTE after orthopaedic surgery. Notably, a

score > 10 predicts increased risk, with 5 points for lower extremity fracture, elective arthroplasty, or polytrauma[166]. This risk is reflected in current practice, as survey data indicates that 76% of orthopaedic surgeons recommended chemical DVT prophylaxis in foot and ankle fractures[167]. This increases to 86% for tibia fractures, and > 95% for all other lower extremity fractures[167]. Agency for Healthcare Research and Quality (AHRQ) guidelines for VTE prophylaxis define major orthopaedic surgery as total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, and recommend chemical prophylaxis for these operations[168].

Orthopaedic procedures in the upper extremity, lower extremity arthroscopy, and surgery distal to the ankle in patients with isolated injuries have lower VTE risk and can be considered non-major. In a large database study, risk of DVT in patients with upper extremity surgery was 0.2%[169]. In current clinical practice, orthopaedic surgeons recommend chemical anticoagulation in 38% of isolated upper extremity injuries, less frequently than in lower extremity surgeries[167]. Patients undergoing foot and ankle surgery also have rates of VTE less than 1%[170]. However, this risk is higher in patients undergoing foot and ankle surgery for orthopaedic trauma – especially in cases where chemical prophylaxis is not used (up to 36%)[170]. Despite the higher overall occurrence of VTE in foot and ankle trauma patients, the actual rate of proximal DVT was significantly lower – ranging between 0.9 - 6.4%. In a meta-analysis of patients undergoing knee arthroscopy, only 10 out of 921 had symptomatic DVT without anticoagulation[171]. Reflecting this data, the American College of Chest Physicians guidelines recommend no chemical VTE prophylaxis after knee arthroscopy, due to low rate of DVT and equivalent risk of bleeding complications[172].

While anatomic location of surgery is an important predictor of post-operative DVT, additional factors must be considered when defining major surgery. Notably, length of surgery and expected patient mobility post-operatively must be considered when defining VTE risk[161,173-175].

Justin E. Kleiner, Marc F. Swiontkowski, Paul Tornetta III

References

153. Drescher FS, Sirovich BE, Lee A, Morrison DH, Chiang WH, Larson RJ. Aspirin versus anticoagulation for prevention of venous thromboembolism major lower extremity orthopedic surgery: a systematic review and meta-analysis. J Hosp Med. 2014 Sep;9(9):579-85.

154. Fisher W. Managing hip fracture and lower limb surgery in the emergency setting: Potential role of non-vitamin K antagonist oral anticoagulants. J Trauma Acute Care Surg. 2017 Jun;82(6):1112-21.

155. Morais QCD, Santos MS. Multi-Criteria Model for Evaluating Drugs to Prevent Deep Venous Thrombosis Associated With Orthopedic Surgery: A Hospital-Based Case Study. Value Health Reg Issues. 2020 Dec;23: 105-11.

156. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019 Dec 10;3(23):3898-944.

157. Pan Y, Mei J, Wang L, Shao M, Zhang J, Wu H, Zhao J. Investigation of the Incidence of Perioperative Pulmonary Embolism in Patients with Below-Knee Deep Vein Thrombosis after Lower Extremity Fracture and Evaluation of Retrievable Inferior Vena Cava Filter Deployment in These Patients. Ann Vasc Surg. 2019 Oct; 60:45-51.

158. Villarreal JV, Shibuya N, Jupiter DC. Thromboprophylaxis and Bleeding Complications in Orthopedic and Trauma Patients: A Systematic Review. J Foot Ankle Surg. 2021 Sep-Oct;60(5):1014-22.

159. Wæver D, Lewis D, Saksø H, Borris LC, Tarrant S, Thorninger R. The Effectiveness and Safety of Direct Oral Anticoagulants Following Lower Limb Fracture Surgery: A Systematic Review and Meta-analysis. J Orthop Trauma. 2021 Apr 1; 35(4):217-24.

160. 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 Aug 3;15(8):e0235628.

161. Haac BE, O'Hara NN, Mullins CD, Stein DM, Manson TT, Johal H, Castillo R, O'Toole RV, Slobogean GP. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. BMJ Open. 2017 Aug 11;7(8): e016676.

162. Nederpelt CJ, Breen KA, El Hechi MW, Krijnen P, Huisman MV, Schipper IB, Kaafarani HMA, Rosenthal MG. Direct Oral Anticoagulants Are a Potential Alternative to Low-Molecular-Weight Heparin for Thromboprophylaxis in Trauma Patients Sustaining Lower Extremity Fractures. J Surg Res. 2021 Feb; 258:324-31.

163. Patterson JT, Morshed S. Chemoprophylaxis for Venous Thromboembolism in Operative Treatment of Fractures of the Tibia and Distal Bones: A Systematic Review and Meta-analysis. J Orthop Trauma. 2017 Sep;31(9):453-60.

164. Farfan M, Bautista M, Bonilla G, Rojas J, Llinás A, Navas J. Worldwide adherence to ACCP guidelines for thromboprophylaxis after major orthopedic surgery: A systematic review of the literature and meta-analysis. Thromb Res. 2016 May;141:163-70.

165. Kanchanabat B, Stapanavatr W, Meknavin S, Soorapanth C, Sumanasrethakul C, Kanchanasuttirak P. Systematic review and meta-analysis on the rate of postoperative venous thromboembolism in orthopaedic surgery in Asian patients without thromboprophylaxis. Br J Surg. 2011 Oct;98(10):1356-64.

166. Dashe J, Parisien RL, Pina M, De Giacomo AF, Tornetta P 3rd. Is the Caprini Score Predictive of Venothromboembolism Events in Orthopaedic Fracture Patients? J Orthop Trauma. 2019 Jun;33(6):269-75.

167. Sagi HC, Ahn J, Ciesla D, Collinge C, Molina C, Obremskey WT, Guillamondegui O, Tornetta P 3rd; Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee. Venous Thromboembolism Prophylaxis in Orthopaedic Trauma Patients: A Survey of OTA Member Practice Patterns and OTA Expert Panel Recommendations. J Orthop Trauma. 2015 Oct; 29(10):e355-62.

168. Balk EM, Ellis AG, Di M, Adam GP, Trikalinos TA. Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update. Agency for Healthcare Research and Quality (US); 2017. Accessed August 28, 2021. http://www.ncbi.nlm.nih.gov/books/NBK476632/

169. Whiting PS, White-Dzuro GA, Greenberg SE, VanHouten JP, Avilucea FR, Obremskey WT, Sethi MK. Risk Factors for Deep Venous Thrombosis Following Orthopaedic Trauma Surgery: An Analysis of 56,000 patients. Arch Trauma Res. 2016 Jan 23;5(1):e32915.

170. Mangwani J, Sheikh N, Cichero M, Williamson D. What is the evidence for chemical thromboprophylaxis in foot and ankle surgery? Systematic review of the English literature. Foot (Edinb). 2015 Sep;25(3):173-8.

171. Perrotta C, Chahla J, Badariotti G, Ramos J. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. Cochrane Database Syst Rev. 2020 May 6;5:CD005259.

172. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

173. McLiesh P, Wiechula R. Identifying and reducing the incidence of post discharge Venous Thromboembolism (VTE) in orthopaedic patients: a systematic review. JBI Libr Syst Rev. 2012;10(28)(Suppl):1-14.

174. Sobieraj DM, Coleman CI, Tongbram V, Chen W, Colby J, Lee S, Kluger J, Makanji S, Ashaye A, White CM. Comparative effectiveness of combined pharmacologic and mechanical thromboprophylaxis versus either method alone in major orthopedic surgery: a systematic review and meta-analysis. Pharmacotherapy. 2013 Mar;33(3):275-83.

175. Sobieraj DM, Lee S, Coleman CI, Tongbram V, Chen W, Colby J, Kluger J, Makanji S, Ashaye AO, White CM. Prolonged versus standard-duration venous thromboprophylaxis in major orthopedic surgery: a systematic review. Ann Intern Med. 2012 May 15;156(10):720-7.

6 - Is routine VTE prophylaxis indicated in patients with a single lower extremity fracture who do not require surgery?

Response/Recommendation: Routine venous thromboembolism (VTE) prophylaxis is not routinely needed in patients with a single lower extremity (LE) fracture who do not require surgery. The need for VTE prophylaxis in patients with isolated LE fracture is restricted to high-risk individuals with significant medical comorbidities, severely limited activity or other coagulopathic risk factors.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.65% Disagree 4.35% Abstain 0.00% (Strong Consensus).

Rationale: Fractures of the LE are common, with an annual incidence of approximately 17% to 22%[176,177]. The incidence of these fractures is increasing[178], and a significant proportion of these fractures are managed non-operatively, most commonly with cast immobilization[179,180]. The incidence of VTE in patients with isolated LE fracture who do not require surgery is low, with reported rates of 0.1% to 4%, leading most to believe that there is no need for routine thromboprophylaxis in this patient population[181-184].

An interesting finding amongst patients with LE injuries is that compared to foot and ankle fractures, acute achilles tendon ruptures have a relatively greater incidence of developing VTE[182,185], probably due to dysfunction of the calf muscle pump. Contrary to popular belief, active ankle and toe movements and compression stockings did not reduce VTE incidence and are not viable strategies for preventing VTE[186,187]. Existing literature remains inconclusive with regards to the need for thromboprophylaxis for patients receiving this mode of management.

The American College of Chest Physicians (ACCP) guidelines does not recommend any prophylaxis for isolated LE fractures requiring immobilization[188]. Jameson et al., after retrospectively analyzing 14,777 adults over a 54-month period, stated that isolated ankle fractures not requiring surgery is not an indication for routine VTE prophylaxis[189]. In addition, Selby et al., found routine prophylaxis to be less favorable for these patients[190] following analysis based on their prospective multicenter study. In contrast, other studies have demonstrated that prophylaxis significantly reduces VTE incidence and related events in patients with isolated LE fractures treated with immobilization[181-195]. Assessment of risk factors and developing clinical risk assessment models predicting VTE in these patients would therefore improve the evidence gap in this domain.

Few studies have sought to assess risk factors and patients at risk for developing VTE following non-surgical treatment for isolated LE fractures[196-198]. Age > 70 years, limited mobility in and out of hospital[196], immobilization[197,198], previous history of VTE, high body mass index (BMI), oral contraceptive pill intake, and air-travel[198] have been reported as risk factors, particularly when two or more are present. The thrombosis risk prediction following cast immobilization (L-TRiP) score[199] and the trauma, immobilization, and patients' characteristics (TIP) score[200] are useful tools for accurately stratifying patients into risk categories in order to guide thromboprophylaxis. The evidence base for the optimal choice of pharmacological prophylaxis in these patients varies with low-molecular-weight heparin (LMWH)[194,195], and oral anticoagulants (such as nadroparin or fondaparinux or rivaroxaban)[191,201] being shown to be effective in preventing VTE and related events.

Based on available literature, administration of routine VTE prophylaxis for patients with isolated LE injuries, even if immobilized, does not seem to be supported. However, VTE prophylaxis in the forms of mechanical or chemical treatment may need to be considered for high-risk patients (see risk stratification) with isolated LE injury.

Abtin Alvand, Raja Bhaskara Rajasekaran, Marc F. Swiontkowski

References

176. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd. Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res. 2014 Mar; 29(3):581-9.

177. Lambers K, Ootes D, Ring D. Incidence of patients with lower extremity injuries presenting to US emergency departments by anatomic region, disease category, and age. Clin Orthop Relat Res. 2012 Jan;470(1):284-90.

178. Hemmann P, Friederich M, Körner D, Klopfer T, Bahrs C. Changing epidemiology of lower extremity fractures in adults over a 15-year period - a National Hospital Discharge Registry study. BMC Musculoskelet Disord. 2021 May 19;22(1): 456.

179. Jameson SS, Rankin KS, Desira NL, James P, Muller SD, Reed MR, Rangan A. Pulmonary embolism following ankle fractures treated without an operation - an analysis using National Health Service data. Injury. 2014 Aug; 45(8):1256-61.

180. Jain N, Symes T, Doorgakant A, Dawson M. Clinical audit of the management of stable ankle fractures. Ann R Coll Surg Engl. 2008 Sep;90(6):483-7.

181. Jameson SS, Augustine A, James P, Serrano-Pedraza I, Oliver K, Townshend D, Reed MR. Venous thromboembolic events following foot and ankle surgery in the English National Health Service. J Bone Joint Surg Br. 2011 Apr;93(4):490-7.

182. Blanco JA, Slater G, Mangwani J. A Prospective Cohort Study of Symptomatic Venous Thromboembolic Events in Foot and Ankle Trauma: The Need for Stratification in Thromboprophylaxis? J Foot Ankle Surg. 2018 May - Jun;57(3): 484-8.

183. Iqbal HJ, Dahab R, Barnes S. UK national survey of venous thromboembolism prophylaxis in ankle fracture patients treated with plaster casts. Foot Ankle Surg. 2012 Sep;18(3):157-9.

184. Roberts C, Horner D, Coleman G, Maitland L, Curl-Roper T, Smith R, Wood E, Mackway-Jones K. Guidelines in Emergency Medicine Network (GEMNet): guideline for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation. Emerg Med J. 2013 Nov;30(11): 968-82.

185. Braithwaite I, De Ruyter B, Semprini A, Ebmeier S, Kiddle G, Willis N, Carter J, Weatherall M, Beasley R. Cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism. BMJ Open. 2016 Oct 4;6(10):e012764.

186. Hickey BA, Cleves A, Alikhan R, Pugh N, Nokes L, Perera A. The effect of active toe movement (AToM) on calf pump function and deep vein thrombosis in patients with acute foot and ankle trauma treated with cast - A prospective randomized study. Foot Ankle Surg. 2017 Sep;23(3):183-8.

187. Sultan MJ, Zhing T, Morris J, Kurdy N, McCollum CN. Compression stockings in the management of fractures of the ankle: a randomised controlled trial. Bone Joint J. 2014 Aug;96-B(8):1062-9.

188. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

189. Jameson SS, Rankin KS, Desira NL, James P, Muller SD, Reed MR, Rangan A. Pulmonary embolism following ankle fractures treated without an operation - an analysis using National Health Service data. Injury. 2014 Aug;45(8):1256-61.

190. Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F. Symptomatic venous thromboembolism uncommon without thromboprophylaxis after isolated lower-limb fracture: the knee-to-ankle fracture (KAF) cohort study. J Bone Joint Surg Am. 2014 May 21;96(10):e83.

191. Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ; PROTECT studygroup. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017 Apr;48(4):936-40.

192. Hickey BA, Watson U, Cleves A, Alikhan R, Pugh N, Nokes L, Perera A. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. Foot Ankle Surg. 2018 Feb;24(1):19-27.

193. Samama CM, Lecoules N, Kierzek G, Claessens YE, Riou B, Rosencher N, Mismetti P, Sautet A, Barrellier MT, Apartsin K, Jonas M, Caeiro JR, van der Veen AH, Roy PM; FONDACAST Study Group. Comparison of fondaparinux with low molecular weight heparin for venous thromboembolism prevention in patients requiring rigid or semi-rigid immobilization for isolated non-surgical below-knee injury. J Thromb Haemost. 2013 Oct;11(10):1833-43.

194. Testroote M, Stigter WA, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database Syst Rev. 2014 Apr 25;(4):CD006681.

195. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database Syst Rev. 2017 Aug 6;8:CD006681.

196. Braithwaite I, Healy B, Cameron L, Weatherall M, Beasley R. Lower limb immobilisation and venous thromboembolism risk: combined case-control studies. Postgrad Med J. 2017 Jun;93(1100):354-9.

197. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. J Thromb Haemost. 2014;12(3):290-6.

198. Mangwani J, Sheikh N, Cichero M, Williamson D. What is the evidence for chemical thromboprophylaxis in foot and ankle surgery? Systematic review of the English literature. Foot (Edinb). 2015 Sep;25(3):173-8.

199. Nemeth B, van Adrichem R, Nelissen R, le Cessie S, Cannegieter SC. Individualized Thromboprophylaxis in Patients with Lower-Leg Cast Immobilization-A Validation and Subgroup Analysis in the POT-CAST Trial. Thromb Haemost. 2019 Sep;119(9):1508-16.

200. Douillet D, Nemeth B, Penaloza A, Le Gal G, Moumneh T, Cannegieter SC, Roy PM. Venous thromboembolism risk stratification for patients with lower limb trauma and cast or brace immobilization. PLoS One. 2019 Jun 20;14(6):e0217748.

201. Haque S, Davies MB. Oral thromboprophylaxis in patients with ankle fractures immobilized in a below the knee cast. Foot Ankle Surg. 2015 Dec;21(4):266-8.

7 - Is routine VTE prophylaxis indicated in patients with immobilization of the lower extremity (e.g., casting) without surgery?

Response/Recommendation: Routine venous thromboembolic (VTE) prophylaxis is not indicated in patients with immobilization of the lower extremity.

Strength of the Recommendation: Moderate.

Delegates vote: Agree 86.96% Disagree 10.87% Abstain 2.17% (Strong Consensus).

Rationale: Patients with cast immobilization of the lower extremity may be at an increased risk for developing VTE. Based on one study, patients not receiving thromboprophylaxis have a pooled absolute risk for asymptomatic events of 18.0% (95% confidence interval [CI] 12.9 to 23.1) and a symptomatic risk of 2.0% (95% CI 1.3 to 2.7) (within approximately 3-months)[202].

The effectiveness of thromboprophylaxis for the prevention of VTE in these patients has been addressed in multiple small randomized controlled trials (RCT), focusing on asymptomatic events in the past. All trials allocated patients to either no therapy or low-molecular-weight heparin (LMWH). Patients were managed with various types of casts, for a variety of non-surgical problems (fractures treated conservatively, tendon ruptures, and so on). In one of the earlier trials, performed in 1993, 253 patients, aged > 16 years were recruited and conservatively managed with a lower limb cast for at least 7 days[203]. Patients were randomized between nadroparin or no treatment for 16 days. In the protocol analysis, after 53 post-randomization exclusions, 4.8% of all patients with prophylaxis, and 16.5% of patients without prophylaxis developed asymptomatic deep venous thrombosis (DVT) (defined by compression ultrasound) (risk reduction of 11.7% [95% CI 4.3% – 19.3%]). Kock et al., then published a RCT using similar inclusion criteria, in which 339 patients with a lower limb cast were analyzed[204]. Upon cast removal, a compression ultrasound and duplex scanning was performed, and suspected asymptomatic events were confirmed with venography. In this trial, much lower incidences were found; 0% in the treated and 4.3% in the non-treated group developed asymptomatic DVT (risk reduction 4.3% [95% CI 1.2% – 7.4%]).

Two other trials have been published, but patients undergoing surgery and treated non-operatively were included. In one study[205], there was no protective effect of the LMWH (no differences between groups, and no symptomatic DVT in any arm). In the other study[206], a significant reduction in asymptomatic DVT (relative risk [RR] 0,45, 95% CI 0,24 to 0,83), but no significant reduction for symptomatic VTE (RR, 0.08, 95% CI 0.00 to 1.36) was detected.

To verify whether patients with lower limb cast immobilization could benefit from thromboprophylaxis, a multicenter high-quality RCT (POT-CAST trial), powered based on symptomatic VTE reduction, was performed[207]. The trial included 1,519 patients who were assigned to LMWH or no prophylaxis during the full period of immobilization of the lower limb. While most patients (approximately 90%) were treated without surgery, the study did include patients who required surgical intervention. Symptomatic VTE occurred in 10 of the 719 patients (1.4%) in the treatment group and in 13 of the 716 patients (1.8%) in the control group (RR, 0.8; 95% CI, 0.3 to 1.7; absolute difference in risk, -0.4 percentage points; 95% CI, - 1.8 to 1.0). No major bleeding events occurred. The results of this trial indicated that there was no advantage to administration of routine chemoprophylaxis (LMWH) to patients with isolated lower extremity injury that required immobilization.

Several meta-analyses have reviewed the published data on this subject matter[208,209]. In a Cochrane review[208], it was reported that thromboprophylaxis was effective for the prevention of asymptomatic VTE for a pooled RR of 0.49, 95% CI 0.34 to 0.72 (heterogeneity I2 20%, p = 0.29). It is important to note that all of these trials were powered for prevention of asymptomatic VTE and are of limited quality. Thus, based on our understanding of the available literature, we do not believe that routine use of thromboprophylaxis is indicated in patients with immobilization of lower extremity, who are not undergoing surgery. With the exception of the POT-CAST trial, studies suffer from extensive heterogeneity of included patients, weak methodology such as inadequate sample size (underpowered), high rates of loss to follow-up, inclusion of

high-risk patients only, and post-randomization exclusions. The latter may also explain why the American College of Chest Physicians (ACCP) guideline also does not recommend routine chemoprophylaxis for patients with isolated lower limb injuries requiring leg immobilization[210]. Other available guidelines advocate for the use of thromboprophylaxis on an individualized approach by evaluating the risks and benefits of such prophylaxis[211].

Banne Nemeth, Francisco Palma-Arjona, Alberto D. Delgado-Martinez, James W.M. Kigera

References

202. Nemeth B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy. Thromb Res. 2019 Feb;174:62-75.

203. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis. 1993 Mar;23(Suppl 1):20-6.

204. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet. 1995 Aug 19;346(8973):459-61.

205. Jørgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R, Kirchhoff-Jensen R, Kjaer L, Kerbouche N, Leth-Espensen P, Narvestad E, Rasmussen SW, Sloth C, Tørholm C, Wille-Jørgensen P. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thromb Res. 2002 Mar 15;105(6):477-80.

206. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002 Sep 5;347(10):726-30.

207. van Adrichem RA, Nemeth B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC; POT-KAST and POT-CAST Group. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. N Engl J Med. 2017 Feb 9;376(6):515-25.

208. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database Syst Rev. 2017 Aug 6;8:CD006681.

209. Ettema HB, Kollen BJ, Verheyen CCPM, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2008 Jul;6(7):1093-8.

210. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2)(Suppl):e278S-325S.

211. Venous thromboembolism: reducing the risk for patients in hospital | Guidance | NICE. Accessed October 19, 2021. https://www.nice.org.uk/Guidance/CG92

8 - Does the duration of immobilization of patients with lower extremity injuries influence the choice of VTE prophylaxis?

Response/Recommendation: Duration of immobilization in patients with lower extremity injuries does not influence the choice of venous thromboembolism (VTE) prophylaxis.

Strength of Recommendation: Moderate.

Delegates vote: Agree 93.18% Disagree 4.55% Abstain 2.27% (Strong Consensus).

Rationale: Prolonged postoperative immobilization is a well-established risk factor for the development of VTE after surgery[212]. However, the use of VTE prophylaxis in patients who are immobilized following lower-extremity injuries remains a contentious issue[213,214]. The 2012 American College of Chest Physicians (ACCP) guidelines recommend against the routine use of VTE prophylaxis in patients with isolated lower-extremity injuries, including immobilized patients[215]. Despite this, standard practice in Europe is still to routinely administer low-molecular-weight heparin (LMWH) as a method of VTE prophylaxis for all patients immobilized following a lower-extremity injury[216]. Current clinical practice guidelines have yet to reach a consensus on a reliable treatment algorithm in this setting[213,215]. Furthermore, whether the duration of immobilization in these patients should influence the choice of VTE prophylaxis remains inadequately investigated.

LMWH has a well-documented adverse side effect profile[217]. Despite this, it is still commonly used as a method of VTE prophylaxis following lower-extremity injuries[218]. Recent literature has suggested that it may not be as reliable at preventing VTE in these patients as previously believed. In a study by Lapidus et al.[219], participants were randomized to receive either thromboprophylaxis with dalteparin or placebo for 5 weeks after ankle fracture surgery. To be eligible for inclusion, patients had to have received dalteparin for at least 1-week prior to randomization. The mean duration of immobilization was 44 days in both groups. The incidence of radiographically confirmed deep venous thrombosis (DVT) did not significantly differ between the two groups. Additionally, a randomized controlled trial (RCT) by Nemeth et al.[220], demonstrated that patients with below-knee cast immobilization administered LMWH, vs. those receiving placebo, demonstrated comparable rates of VTE occurrence. The average immobilization duration in this study was 4.9 weeks. Similarly, Van Adrichem et al.[221], conducted two separate clinical trials to investigate the efficacy of dalteparin and nadroparin for the prevention of VTE in patients immobilized following either knee arthroscopy, or after casting of the lower leg. The average duration of immobilization was 4.9 weeks. Patients were randomized to receive either dalteparin, nadroparin or no-anticoagulation. They found that patients receiving LMWH, vs. patients in the no-anticoagulation group, demonstrated comparable rates of symptomatic VTE occurrence (1.4% and 1.8%, respectively).

Conversely, several studies have demonstrated LMWH ability to cause a relative risk reduction of VTE in this patient population, regardless of the duration of immobilization. Lassen et al.[222], conducted a clinical trial to evaluate the safety and efficacy of reviparin in patients immobilized for ≥ 5-weeks after a distal leg fracture or achilles tendon rupture. Mean duration of immobilization in the treatment and control groups was 43-days and 44-days, respectively. Radiographically confirmed DVT occurred in 9% of patients randomized to receive reviparin, and 19% of patients randomized to the placebo group. In another study, Otero-Fernandez et al.[223], audited the effectiveness of bemiparin in orthopaedic patients managed both surgically and medically. Patients were stratified to receive high-dose (3,500 IU daily) or low-dose (2,500 IU/daily) bemiparin based on their individual physician's assessment of their risk for developing VTE. 6,456 patients were included,

26% of whom were immobilized by plaster cast. Within this sub-group, mean immobilization and duration of treatment was 12.8 days and 21 days, respectively. Patients placed in a cast had a low rate (0.45%) of symptomatic VTE at 30-days.

Following the advent of newer more potent anticoagulants, several studies have been designed in an effort to investigate their safety and efficacy, when compared to more conventional anticoagulation. In one study, Bruntink et al.[224], conducted a multicenter RCT of patients with an ankle or foot fracture who required immobilization. Patients were randomized to either the no-treatment group, the nadroparin group (2,850 IU once daily), or the fondaparinux group (2.5 mg once daily). Mean duration of immobilization was 40 days for the no-treatment and nadroparin groups, and 38 days for those receiving fondaparinux. The incidence of DVT was 2.2% in the nadroparin group, 1.1% in the fondaparinux group, and 11.7% in the control group ($p = 0.011$). Similarly, Samama et al.[225], reported on a multicenter study comparing efficacy and safety between fondaparinux and nadroparin. 1,349 patients with an isolated non-surgical, unilateral below-knee injury were randomized into either treatment group. Mean immobilization and treatment durations were 32 days in the fondaparinux group, and 34 days in the nadroparin group. The incidence of DVT in the fondaparinux group and nadroparin group was 2.6% and 8.2%, respectively ($p < 0.001$). Additionally, The PROphylaxis in NOn-Major Orthopaedic Surgery (PRONOMOS)[226] clinical trial compared the effect of rivaroxaban versus enoxaparin in preventing major VTE in patients undergoing lower limb non-major orthopaedic surgery. Patients had to have been scheduled to receive VTE prophylaxis for at least 2 weeks to be eligible for enrollment. The primary outcome studied was the occurrence of symptomatic proximal or distal DVT, pulmonary embolism (PE), and VTE-related death during the treatment period, as well as asymptomatic proximal DVT at the end of treatment. The primary outcome occurred in 0.24% of patients in the rivaroxaban group and in 1.10% of patients in the enoxaparin group ($p < 0.05$). Bleeding rates were comparable between the rivaroxaban and enoxaparin groups (1.08% and 1.04%, respectively). In conclusion, rivaroxaban proved more effective than enoxaparin in preventing VTE events during a period of immobilization after non-major orthopaedic surgery of the lower limbs, regardless of the duration of immobilization.

The likelihood of VTE complications occurring postoperatively depends on a dynamic interplay between both patient-related and nonpatient-related factors[227]. Studies have repeatedly shown that prolonged postoperative immobilization does definitively increase a patient's risk of developing VTE complications[228]. Guidelines on early and aggressive postoperative mobilization have been established to mitigate the risks it poses to patients[229]. Currently, the duration of immobilization in patients with lower extremity injuries does not appear to influence the choice of VTE prophylaxis.

Aydin Gahramanov, Saad Tarabichi, Charles-Marc Samama

References

212. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23)(Suppl 1):I9-16.

213. Testroote M, Stigter WA, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. In: The Cochrane Collaboration,ed., ed Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2014:CD006681.pub3.

214. Ettema HB, Kollen BJ, Verheyen CCPM, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2008 Jul; 6(7):1093-8.

215. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

216. Ageno W, Dentali F, Imberti D. A survey of thrombosis prophylaxis use in patients with lower limb fractures. Thromb Haemost. 2004 Nov;92(5): 1166-7.

217. Gouin-Thibault I, Pautas E, Siguret V. Safety profile of different low-molecular weight heparins used at therapeutic dose. Drug Saf. 2005;28(4):333-49.

218. Zufferey P, Laporte S, Quenet S, Molliex S, Auboyer C, Decousus H, Mismetti P. Optimal low-molecular-weight heparin regimen in major orthopaedic surgery. A meta-analysis of randomised trials. Thromb Haemost. 2003 Oct; 90(4):654-61.

219. Lapidus LJ, Ponzer S, Elvin A, Levander C, Lärfars G, Rosfors S, de Bri E; Lapidus. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta Orthop. 2007 Aug;78(4):528-35.

220. Nemeth B, van Adrichem R, Nelissen R, le Cessie S, Cannegieter SC. Individualized Thromboprophylaxis in Patients with Lower-Leg Cast Immobilization-A Validation and Subgroup Analysis in the POT-CAST Trial. Thromb Haemost. 2019 Sep;119(9):1508-16.

221. van Adrichem RA, Nemeth B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC; POT-KAST and POT-CAST Group. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. N Engl J Med. 2017 Feb 9;376(6):515-25.

222. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002 Sep 5;347(10):726-30.

223. Otero-Fernández R, Gómez-Outes A, Martínez-González J, Rocha E, Fontcuberta J; Bemiparin Cooperative Study Group in Orthopaedic Patients. Evaluation of the effectiveness and safety of bemiparin in a large population of orthopedic patients in a normal clinical practice. Clin Appl Thromb Hemost. 2008 Jan;14(1):75-83.

224. Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ; PROTECT studygroup. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017 Apr;48(4):936-40.

225. Samama CM, Lecoules N, Kierzek G, Claessens YE, Riou B, Rosencher N, Mismetti P, Sautet A, Barrellier MT, Apartsin K, Jonas M, Caeiro JR, van der Veen AH, Roy PM; FONDACAST Study Group. Comparison of fondaparinux with low molecular weight heparin for venous thromboembolism prevention in patients requiring rigid or semi-rigid immobilization for isolated non-surgical below-knee injury. J Thromb Haemost. 2013 Oct;11(10):1833-43.

226. Samama CM, Laporte S, Rosencher N, Girard P, Llau J, Mouret P, Fisher W, Martínez-Martín J, Duverger D, Deygas B, Presles E, Cucherat M, Mismetti P; PRONOMOS Investigators. Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery. N Engl J Med. 2020 May 14;382(20):1916-25.

227. Laryea J, Champagne B. Venous thromboembolism prophylaxis. Clin Colon Rectal Surg. 2013 Sep;26(3):153-9.

228. Braithwaite I, Healy B, Cameron L, Weatherall M, Beasley R. Lower limb immobilisation and venous thromboembolism risk: combined case-control studies. Postgrad Med J. 2017 Jun;93(1100):354-9.

229. Pearse EO, Caldwell BF, Lockwood RJ, Hollard J. Early mobilisation after conventional knee replacement may reduce the risk of postoperative venous thromboembolism. J Bone Joint Surg Br. 2007 Mar;89(3):316-22.

9 - What is the most optimal VTE prophylaxis for patients undergoing internal fixation of a hip fracture?

Response/Recommendation: Mechanical and pharmacological venous thromboembolism (VTE) prophylaxes are

advised for patients undergoing internal fixation of a hip fracture, following an individualized risk assessment. In the setting of surgical delays, preoperative pharmacological prophylaxis should be considered. Pharmacological thromboprophylaxis should continue throughout the persistent postoperative prothrombotic state, commencing 12 hours post wound closure, and continuing for at least 28 days.

Strength of Recommendation: Moderate

Delegates vote: Agree 95.56% Disagree 2.22% Abstain 2.22% (Strong Consensus).

Rationale: Patients sustaining hip fracture are subjected to a risk of VTE quoted at over 30% within the literature[230-233]. Advancements in thromboprophylaxis have reduced the overall rates of clinically relevant VTE to less than 4%[234-237]. The goals of VTE prophylaxis within this at-risk cohort are to prevent fatal pulmonary embolism (PE) and reduce the incidence of post-VTE morbidity, both of which contribute to the significant in-hospital and one-year mortality rates[238-240]. Despite widespread awareness of the merits of thromboprophylaxis, variability in practice patterns persist, owing to a lack of available high-quality evidence[241-244]. As such, published clinical practice guidelines (CPG) have made efforts to highlight the standards required of healthcare providers so as to mitigate VTE risk within the hip fracture population[235,244-247].

On admission, it is advised that hip fracture patients undergo medical optimization, adequate hydration and receive mechanical prophylaxis, using graduated compression stockings (GCS) or intermittent pneumatic compression devices (IPCD), ensuring correct application, provided no contraindications are identified[235,245,246,248,249]. Pharmacological prophylaxis should be considered preoperatively if surgical delays are anticipated, commenced ideally within 14 hours of admission, following a comprehensive bleeding and thrombosis risk assessment[250]. Appropriate preoperative agents include either low-molecular-weight heparin (LMWH), with the last dose administered no less than 12 hours preoperatively, or unfractionated heparin (UFH) with close serological monitoring, particularly in patients requiring weight or renal adjusted formulations[245,250,251]. Fondaparinux use has been historically suggested, however its use has been more recently cautioned preoperatively given its known protracted onset of action, and the need for 24 hours to ensure adequate pharmacological clearance. In addition to mechanical and chemical thromboprophylaxis, early definitive internal fixation is favored, so as to mitigate the crescendo effect of delayed surgical intervention on VTE risk, whilst also minimizing the period of preoperative bed-rest[234,252,253].

Postoperatively, mechanical prophylaxis should take the form of early mobilization, coupled with continuous GCS or IPCD use for the duration of stay in both the acute hospital and post-discharge rehabilitation settings[247,248,254,255]. Choice of GCS length, either knee-length or thigh-length, should rely on patient compliance, preference and local skin condition, as no significant difference has been identified to date between either in preventing postoperative VTE[256]. Mechanical prophylaxis has also been advised to continue, for at least 18 hours per day, until a level of mobility is achieved resembling the patient's pre-admission status[245,248,249].

The published CPG all agree that pharmacological prophylaxis, in combination with mechanical prophylaxis, is required to prevent fatal PE and post-VTE morbidity. Postoperatively, it is suggested that the first prophylactic dose should be administered no sooner than 12 hours post wound closure[245,247,257,258]. Agents proven to be efficacious in the setting of hip fractures include LMWH, UFH, fondaparinux, adjusted-dose vitamin K antagonists and aspirin (ASA)[253]. Agent selection should be based on patient parameters, healthcare provider preferences and a shared decision. Therapy should continue for a minimum of 10 to 14 days, with most recommendations within CPG to continue for at least 28 to 35 days postoperatively, in light of the persistently elevated postoperative VTE risk[233,236,245,247,257,259,260]. LMWH or UFH are often utilized in the early postoperative period in clinical practice, given their parenteral preparations and reliable pharmacokinetics[234].

To date, a leading pharmacological agent has yet to be defined. LMWH has been established as the prophylactic agent against which novel medications are compared[235]. The American College of Chest Physicians (ACCP), and the American Society of Hematology (ASH) guidelines both specifically advocate for a full extended prophylactic course of LMWH in the setting of a hip fracture, despite surgeon reservations surrounding the need for administration education, as well as the inconvenience of daily subcutaneous injections[235,247]. Fondaparinux has demonstrated equivocal VTE rates to LMWH, but has been cautioned in light of major bleeding rates experienced by frail patients weighing less than 50 kilograms[235,261]. Warfarin, a vitamin K antagonist, has not demonstrated significant benefits compared to LMWH in the hip fracture population to date. Safety concerns with warfarin remain, particularly in relation to management of the international normalized ratio (INR) perioperatively, contributions to surgical delays due to prolonged clearance, slow onset on action, and drug interactions affecting its efficacy[234,235,258,262,263]. Rivaroxaban, dabigatran and apixaban have been approved for use against VTE in the setting of total joint arthroplasty but have not yet been sufficiently evaluated in the setting of hip fractures. Recent studies, one of retrospective nature, and one randomized controlled trial with small sample sizes in all study groups, demonstrated encouraging results with direct oral anticoagulant (DOAC) use, however further evidence is required before clinical practice is influenced[264,265]. ASA has been shown to significantly reduce VTE rates throughout the high-risk post fracture time period compared to placebo, but routine ASA use remains controversial, given the lack of evidence to support equivalence to LMWH proven efficacy[266,267]. ASA and DOAC use have come under investigation of late. Two heterogenous meta-analyses, recently published, suggest favorable findings with regards to VTE reduction, however level one evidence is yet to emerge[268,269]. Both agents are convenient given their more

simplistic oral regimens and encouragingly low rates of VTE, but reservations persist concerning hemorrhagic events, particularly in the immediate postoperative period[263,270].

A clear consensus amongst CPG is unfortunately lacking regarding the optimal pharmacological agent, dose and duration. Concerns surround balancing the susceptibility of hip fracture patients to VTE, with the rate of wound complications and significant hemorrhagic events[271]. Despite recent advancements in enhanced recovery programs, clinical care pathways and national audit programs, which have combined to improve the standard of hip fracture care worldwide, VTE CPG continue to reference evidence stemming from the 1990's and 2000's. As such, focusing future research efforts on well-designed high-quality trials is of utmost importance, so as to clarify a consensus on means to reliably prevent VTE in the hip fracture population, and facilitate the publication of guidelines that will positively influence clinical practice.

Andrew J. Hughes, Dheenadhayalan Jayaramaraju, Svetlana A. Bozhkova, Aleksandar R. Lešić, Nagashree Vasudeva, Alina Kasimova, Velmurugesan P. Sundaram, Jaimo Ahn, Chad A. Krueger

References

230. Pedersen AB, Ehrenstein V, Szépligeti SK, Sørensen HT. Excess risk of venous thromboembolism in hip fracture patients and the prognostic impact of comorbidity. Osteoporos Int. 2017 Dec;28(12):3421-30.

231. Nakase J, Toribatake Y, Mouri Y, Seki H, Kitaoka K, Tomita K. Heparin versus danaproid for prevention of venous thromboembolism after hip surgery. J Orthop Surg (Hong Kong). 2009 Apr;17(1):6-9.

232. Eriksson BI, Lassen MR; PENTasaccharide in HIp-FRActure Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2003 Jun 9;163(11):1337-42.

233. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3)(Suppl):338S-400S.

234. Ricci WM, Broekhuyse H, Keating JF, Teague DC, White TO. Thromboprophylaxis an update of current practice: Can we reach a consensus? OTA Int. 2019 Nov 22;2(4):e027.

235. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

236. Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM; ESCORTE group. Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. J Thromb Haemost. 2005 Sep;3(9):2006-14.

237. MacDonald DRW, Neilly D, Schneider PS, Bzovsky S, Sprague S, Axelrod D, Poolman RW, Frihagen F, Bhandari M, Swiontkowski M, Schemitsch EH, Stevenson IM; FAITH Investigators; HEALTH Investigators. Venous Thromboembolism in Hip Fracture Patients: A Subanalysis of the FAITH and HEALTH Trials. J Orthop Trauma. 2020 Nov;34(Suppl 3):S70-5.

238. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. J Clin Med. 2020 Aug 1;9(8):E2467.

239. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture - a systematic review. World J Orthop. 2019 Mar 18;10(3):166-75.

240. Lawrence VA, Hilsenbeck SG, Noveck H, Poses RM, Carson JL. Medical complications and outcomes after hip fracture repair. Arch Intern Med. 2002 Oct 14; 162(18):2053-7.

241. Sagi HC, Ahn J, Ciesla D, Collinge C, Molina C, Obremskey WT, Guillamondegui O, Tornetta P 3rd; Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee. Venous Thromboembolism Prophylaxis in Orthopaedic Trauma Patients: A Survey of OTA Member Practice Patterns and OTA Expert Panel Recommendations. J Orthop Trauma. 2015 Oct;29(10):e355-62.

242. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database Syst Rev. 2002;(4):CD000305.

243. Alsawadi A, Loeffler M. Graduated compression stockings in hip fractures. Ann R Coll Surg Engl. 2012 Oct;94(7):463-71.

244. Scottish Intercollegiate Guidelines Network. Management of Hip Fracture in Older People: A National Clinical Guideline. Scottish Intercollegiate Guidelines Network; 2009.

245. Overview | Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism | Guidance | NICE. Accessed October 21, 2021. https://www.nice.org.uk/guidance/NG89

246. hip-fractures-elderly-clinical-practice-guideline-4-24-19–2.pdf. Accessed October 21, 2021. https://www.aaos.org/globalassets/quality-and-practice-resources/hip-fractures-in-the-elderly/hip-fractures-elderly-clinical-practice-guideline-4-24-19–2.pdf

247. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019 Dec 10;3(23): 3898-944.

248. Amarase C, Tanavalee A, Larbpaiboonpong V, Lee MC, Crawford RW, Matsubara M, Zhou Y; Asia-Pacific (AP) Region Venous Thromboembolism (VTE) Consensus Group. Asia-Pacific venous thromboembolism consensus in knee and hip arthroplasty and hip fracture surgery: Part 2. Mechanical venous thromboembolism prophylaxis. Knee Surg Relat Res. 2021 Jun 30;33(1):20.

249. Mehta KV, Lee HC, Loh JSY. Mechanical thromboprophylaxis for patients undergoing hip fracture surgery. J Orthop Surg (Hong Kong). 2010 Dec;18(3):287-9.

250. Perioperative care overview - NICE Pathways. Accessed October 1, 2021. https://pathways.nice.org.uk/pathways/perioperative-care

251. Overview | Venous thromboembolism in adults | Quality standards | NICE. Accessed October 21, 2021. https://www.nice.org.uk/guidance/qs201

252. Smith EB, Parvizi J, Purtill JJ. Delayed surgery for patients with femur and hip fractures-risk of deep venous thrombosis. J Trauma. 2011 Jun;70(6):E113-6.

253. Hughes AJ, Brent L, Biesma R, Kenny PJ, Hurson CJ. The effect of indirect admission via hospital transfer on hip fracture patients in Ireland. Ir J Med Sci. 2019 May;188(2):517-24.

254. Pavon JM, Adam SS, Razouki ZA, McDuffie JR, Lachiewicz PF, Kosinski AS, Beadles CA, Ortel TL, Nagi A, Williams JW Jr. Effectiveness of Intermittent Pneumatic Compression Devices for Venous Thromboembolism Prophylaxis in High-Risk Surgical Patients: A Systematic Review. J Arthroplasty. 2016 Feb;31(2):524-32.

255. Gill SK, Pearce AR, Everington T, Rossiter ND. Mechanical prophylaxis, early mobilisation and risk stratification: as effective as drugs for low risk patients undergoing primary joint replacement. Results in 13,384 patients. Surgeon. 2020 Aug;18(4):219-25.

256. Sajid MS, Desai M, Morris RW, Hamilton G. Knee length versus thigh length graduated compression stockings for prevention of deep vein thrombosis in postoperative surgical patients. Cochrane Database Syst Rev. 2012 May 16;(5): CD007162.

257. Clinical Guides. Thrombosis Canada - Thrombose Canada. Published April 8, 2013. Accessed October 21, 2021. https://thrombosiscanada.ca/clinicalguides/

258. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e326S-50S.

259. Fisher WD, Agnelli G, George DJ, Kakkar AK, Lassen MR, Mismetti P, Mouret P, Turpie AG. Extended venous thromboembolism prophylaxis in patients undergoing hip fracture surgery - the SAVE-HIP3 study. Bone Joint J. 2013 Apr;95-B(4):459-66.

260. Bjørnarå BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. J Bone Joint Surg Br. 2006 Mar; 88(3):386-91.

261. Eriksson BI, Bauer KA, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001 Nov 1;345(18):1298-304.

262. Mismetti P, Laporte S, Zufferey P, Epinat M, Decousus H, Cucherat M. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. J Thromb Haemost. 2004 Jul;2(7):1058-70.

263. Thiengwittayaporn S, Budhiparama N, Tanavalee C, Tantavisut S, Sorial RM, Li C, Kim KI; Asia-Pacific (AP) Region Venous Thromboembolism (VTE) Consensus Group. Asia-Pacific venous thromboembolism consensus in knee and hip arthroplasty and hip fracture surgery: Part 3. Pharmacological venous thromboembolism prophylaxis. Knee Surg Relat Res. 2021 Aug 12;33(1):24.

264. Goh EL, Gurung PK, Ma S, Pilpel T, Dale JH, Kannan A, Anand S. Direct Oral Anticoagulants in the Prevention of Venous Thromboembolism Following Surgery for Hip Fracture in Older Adults: A Population-Based Cohort Study. Geriatr Orthop Surg Rehabil. 2020 Jan 13;11:2151459319897520.

265. Tang Y, Wang K, Shi Z, Yang P, Dang X. A RCT study of Rivaroxaban, low-molecular-weight heparin, and sequential medication regimens for the prevention of venous thrombosis after internal fixation of hip fracture. Biomed Pharmacother. 2017 Aug;92:982-8.

266. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet. 2000 Apr 15; 355(9212):1295-302.

267. Huang Q, Xing SX, Zeng Y, Si HB, Zhou ZK, Shen B. Comparison of the Efficacy and Safety of Aspirin and Rivaroxaban Following Enoxaparin Treatment for Prevention of Venous Thromboembolism after Hip Fracture Surgery. Orthop Surg. 2019 Oct; 11(5):886-94.

268. Wæver D, Lewis D, Saksø H, Borris LC, Tarrant S, Thorninger R. The Effectiveness and Safety of Direct Oral Anticoagulants Following Lower Limb Fracture Surgery: A Systematic Review and Meta-analysis. J Orthop Trauma. 2021 Apr 1; 35(4):217-24.

269. Hu B, Jiang L, Tang H, Hu M, Yu J, Dai Z. Rivaroxaban versus aspirin in prevention of venous thromboembolism following total joint arthroplasty or hip fracture surgery: a meta-analysis. J Orthop Surg Res. 2021 Feb 13;16(1):135.

270. Flevas DA, Megaloikonomos PD, Dimopoulos L, Mitsiokapa E, Koulouvaris P, Mavrogenis AF. Thromboembolism prophylaxis in orthopaedics: an update. EFORT Open Rev. 2018 Apr 27;3(4):136-48.

271. Muscatelli SR, Charters MA, Hallstrom BR. Time for an Update? A Look at Current Guidelines for Venous Thromboembolism Prophylaxis After Hip and Knee Arthroplasty and Hip Fracture. Arthroplast Today. 2021 Jul 15;10: 105-7.

10 - What is the optimal VTE prophylaxis for patients undergoing arthroplasty (hemiarthroplasty or total hip arthroplasty) for patients with hip fracture?

Response/Recommendation: Hip fracture patients treated with arthroplasty are at higher risk of venous thromboembolism (VTE) and should receive some form of chemothromboprophylaxis. Studies demonstrate that aspirin (ASA) is an effective agent for prevention of VTE in this patient's population.

Strength of Recommendation: Strong.

Delegates vote: Agree 84.78% Disagree 8.70% Abstain 6.52% (Strong Consensus).

Rationale: Hip fracture is one of the most common orthopaedic conditions worldwide, which is associated with 1.7 to 3.6% rate of deep venous thrombosis (DVT), and 1.1% rate of developing pulmonary embolism (PE)[272,273]. Treatment of the hip fracture with total hip arthroplasty (THA) or hemiarthroplasty (HA) is associated with a higher risk of VTE when compared with treatment by internal fixation (hazard ratio [HR] 2.67, p = 0.02)[274]. Administration of thromboprophylaxis to patients undergoing surgical treatment of hip fracture has been shown to reduce VTE events[275]. Other studies have questioned the need for routine administration of chemoprophylaxis to these patients and advocated prophylaxis in high-risk populations such as those with a history of VTE, elderly patients (> 75 years), women and those receiving HA[276].

From a timing standpoint, one large registry study has shown superiority of prophylactic treatment with low-molecular-weight heparin (LMWH) beginning preoperatively when compared with postoperative initiation of anticoagulation[277]. There are very few studies that specifically address chemoprophylaxis in patients undergoing HA or THA for hip fracture. One such study found that the combination of mechanical prophylaxis combined with fondaparinux was superior to fondaparinux prophylaxis alone[278]. Another study evaluated the role of low-dose ASA for patients with hip fracture undergoing HA or internal fixation and found that administration of low-dose ASA was associated with increased need for blood transfusion and a higher all-cause mortality during the first year after surgery[279]. However, a meta-analysis comparing ASA vs. other thromboprophylaxis showed a statistically nonsignificant trend favoring other anticoagulants (relative risk [RR] = 1.60). The risk of bleeding was found to be considerably lower when ASA was administered vs. other anticoagulants (RR = 0.32)[280]. One of the sentinel studies was the Pulmonary Embolism Prevention (PEP) trial that included 13,356 patients with hip fracture receiving ASA vs. placebo. Administration of ASA to hip fracture patients was found to reduce the risk of VTE by a third[281].

A recent multi-institutional study evaluated 1,141 patients with femoral neck fracture who underwent THA or HA. Patients were allocated into cohorts based on the type of prophylaxis administered that included ASA (n = 454) and other anticoagulants (n = 687). The overall VTE rate was 1.98% for patients receiving ASA, compared to 6.7% for patients receiving other anticoagulants ($p < 0.001$). When controlling for potential confounders in the multivariate analysis, ASA was independently associated with a lower risk of VTE (odds ration [OR] 0.31 95% confidence interval [CI] 0.13 - 0.65; effect size estimate: -1.17; p = 0.003). In addition, patients receiving ASA demonstrated a lower rate of 90 days readmission, and periprosthetic joint infection (PJI). Furthermore, patients administered ASA had a lower rate of allogeneic blood transfusion despite no difference in preoperative hemoglobin levels.

Based on the available literature, it appears that patients with hip fracture undergoing HA or THA are at higher risk of VTE and require prophylaxis. ASA appears to be an effective agent for prevention of VTE in this patient's population.

Stephen L. Kates, Eduardo A. Salvati, Lars G. Johnsen

References

272. Campbell A, Lott A, Gonzalez L, Kester B, Egol KA. Patient-Centered Care: Total Hip Arthroplasty for Displaced Femoral Neck Fracture Does Not Increase Infection Risk. J Healthc Qual. 2020 Jan/Feb;42(1):27-36.

273. Warren JA, Sundaram K, Hampton R, Billow D, Patterson B, Piuzzi NS. Venous thromboembolism rates remained unchanged in operative lower extremity orthopaedic trauma patients from 2008 to 2016. Injury. 2019 Oct;50(10): 1620-6.

274. MacDonald DRW, Neilly D, Schneider PS, Bzovsky S, Sprague S, Axelrod D, Poolman RW, Frihagen F, Bhandari M, Swiontkowski M, Schemitsch EH, Stevenson IM; FAITH Investigators; HEALTH Investigators. Venous Thromboembolism in Hip Fracture Patients: A Subanalysis of the FAITH and HEALTH Trials. J Orthop Trauma. 2020 Nov;34(Suppl 3):S70-5.

275. Li Q, Dai B, Xu J, Yao Y, Song K, Zhang H, Chen D, Jiang Q. Can patients with femoral neck fracture benefit from preoperative thromboprophylaxis?: A prospective randomized controlled trial. Medicine (Baltimore). 2017 Jul;96(29): e7604.

276. Lin YC, Lee SH, Chen IJ, Chang CH, Chang CJ, Wang YC, Chang Y, Hsieh PH. Symptomatic pulmonary embolism following hip fracture: A nationwide study. Thromb Res. 2018 Dec;172:120-7.

277. Leer-Salvesen S, Dybvik E, Dahl OE, Gjertsen JE, EngesæTer LB. Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures. Acta Orthop. 2017 Feb;88(1): 48-54.

278. Tsuda Y, Yasunaga H, Horiguchi H, Fushimi K, Kawano H, Tanaka S. Effects of fondaparinux on pulmonary embolism following hemiarthroplasty for femoral neck fracture: a retrospective observational study using the Japanese Diagnosis Procedure Combination database. J Orthop Sci. 2014 Nov;19(6): 991-6.

279. Kragh AM, Waldén M, Apelqvist A, Wagner P, Atroshi I. Bleeding and first-year mortality following hip fracture surgery and preoperative use of low-dose acetylsalicylic acid: an observational cohort study. BMC Musculoskelet Disord. 2011 Nov 7;12:254.

280. Drescher FS, Sirovich BE, Lee A, Morrison DH, Chiang WH, Larson RJ. Aspirin versus anticoagulation for prevention of venous thromboembolism major lower extremity orthopedic surgery: a systematic review and meta-analysis. J Hosp Med. 2014 Sep;9(9):579-85.

281. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet. 2000 Apr 15; 355(9212):1295-302.

11 - Is routine VTE prophylaxis required for patients with fragility fracture of the pelvis or lower extremity?

Response/Recommendation: Chemoprophylaxis against venous thromboembolism (VTE) is recommended for patients with a fragility fracture of the pelvis or lower extremity as long as the risk of VTE outweighs the risk of bleeding given other medical comorbidities. The use of intermittent pneumatic compression (IPC) devices should be considered for those who cannot receive chemoprophylaxis.

Strength of Recommendation: Low.

Delegates vote: Agree 95.56% Disagree 4.44% Abstain 0.00% (Strong Consensus).

Rationale: Fragility fractures are those fractures which result from low-level trauma, such as a fall from standing height, where mechanical forces would not ordinarily cause a fracture[282]. Patients frequently present with pain and limited mobility but may not be able to recall the inciting event[283]. The treatment spectrum varies from open reduction internal fixation, to percutaneous fixation to non-operative treatment[283].

Only one retrospective study was found with a dedicated focus on VTE in low-energy isolated fractures. In this retrospective review of 1,701 patients by Prensky et al., 71.8% (1,222) of the patients sustained lower extremity fractures. Up to 85.6% of patients with a lower extremity fracture received chemoprophylaxis in the form of low-molecular-weight heparin (LMWH), heparin, or vitamin K antagonists. The number receiving chemoprophylaxis rose to 94% when looking at only patients who sustained a hip or pelvis fracture. There were 19 clinically symptomatic VTE in patients with lower extremity fractures within 90 days of discharge. Seventeen of the 19 VTE occurred in patients with hip or pelvis fracture for an overall VTE rate of 2.6% in patients with hip and pelvis fractures and 0.7% for all other fractures. Female sex and high body mass index (BMI) were found to be statistically significant predictors of VTE[284]. It should be noted that 30.5% of the fractures in this study were classified as hip fractures. Hip fractures are specifically excluded from our recommendation as this question is addressed separately.

There remains a paucity of literature on this topic and the rest of the recommendation is based on studies which did not differentiate between high and low energy trauma. In a survey 103 Orthopaedic Trauma Association (OTA) members, there was no consensus for the modality or duration of VTE prophylactic agent following pelvis or acetabular (P&A) fractures regardless of weight bearing status, need for surgery or type of surgical intervention. In this survey, LMWH and aspirin (ASA) were the two most frequently prescribed chemoprophylaxis for patients receiving VTE prophylaxis[285]. For nonsurgical P&A fractures, 64.7% prescribed LMWH while 19.6% prescribed ASA. For surgically treated P&A fractures, 75.7% prescribed LMWH and 7.8% prescribed ASA[285]. Contrary to practices of American surgeons, surveys of trauma centers in the United Kingdom found that 45% of P&A trauma units do not routinely prescribe chemoprophylaxis post-operatively and 56% do not prescribe chemoprophylaxis for conservatively managed patients[286]; 62% do not use chemoprophylaxis following cast immobilization after lower limb injuries[287].

In a retrospective review of 901 patients who underwent surgical treatment of a fracture below the hip, thromboprophylaxis decreased the risk of post-operative VTE from 6.8% to 2.3%. While the exact mechanism of injury for these is not known, over 50% of the patients sustained an injury from a slip or fall[287,288]. An industry funded prospectively randomized controlled trial (RCT) evaluating IPC devices found that when coupled with LMWH, these devices decreased the rate of VTE from 1.7% (LMWH only) to 0.4% (LMWH combined with IPC) in 1,803 patients undergoing a variety of orthopaedic procedures[289].

A recent systematic review of 15 studies of individual risk of VTE due to lower limb immobilization after injury describes advancing age as the most consistent individual risk following injury type and BMI. However, physicians should take into consideration the limited evidence supporting thromboprophylaxis in these cases[290]. Also, early fixation, before 48 hours of pelvic and lower extremity fractures should be noted as an independent predictor of VTE[291]. Other systematic review of 5 level I studies for surgical management of tibia fractures suggested no routine prophylaxis due to doubtful clinical benefit[292].

With foot and ankle surgery, there is no consensus; some studies do not recommend prophylaxis in outpatient surgery patients without individual risks for VTE or those not requiring immobilization[293-297]. Furthermore, others advise using VTE prophylaxis in long cast immobilization, independent of the previous procedure, until weightbearing or removal[298-300]. However, there is a bias in these studies: VTE events following achilles tendon ruptures are greater than ankle fractures treated surgically or conservatory[301]. American College of Chest Physicians (ACCP) guidelines does not support routine prophylaxis, but IPC is recommended in this field[302].

Further research is needed in the form of high quality prospective RCT to determine the need for VTE prophylaxis in

patients who sustain a fragility fracture of the lower extremity. Although there have been some attempts to create VTE risk assessment tools[303,304], to this day none have been validated or standardized[305]. Until then, risk stratification based on other medical comorbidities should play a role in shared decision making between the surgeon and the patient in determining the need for VTE prophylaxis in these patients. Specifically, patients treated surgically should be separately evaluated from those treated non-operatively and the ability of a patient to frequently mobilize factored into the outcomes[306]. It is important to consider that while chemoprophylaxis has been shown to decrease the incidence of VTE, its impact on all-cause mortality and mortality from PE is up for debate[307-309]. Studies designed to answer this question should delineate symptomatic from asymptomatic VTE events. Additionally, broad use of VTE prophylaxis is not without risks with at least one study demonstrating that the risk of death from major bleeding on LMWH was greater than the mortality from PE avoided by its use[310].

Taylor D'Amore, Guillermo Araujo, Iván J. Salce, Nigel D. Rossiter

References

282. National Institute for Health and Clinical Science. Osteoporosis fragility fracture risk scope. Accessed September 14, 2021. https://www.nice.org.uk/guidance/cg146/documents/osteoporosis-final-scope2

283. Rommens PM, Wagner D, Hofmann A. Fragility Fractures of the Pelvis. JBJS Rev. 2017 Mar 21;5(3):e3.

284. Prensky C, Urruela A, Guss MS, Karia R, Lenzo TJ, Egol KA. Symptomatic venous thrombo-embolism in low-energy isolated fractures in hospitalised patients. Injury. 2013 Aug;44(8):1135-9.

285. Lim PK, Ahn J, Scolaro JA. Venous Thromboembolism Prophylaxis After Pelvic and Acetabular Fractures: A Survey of Orthopaedic Surgeons' Current Practices. J Am Acad Orthop Surg. 2020 Sep 15;28(18):750-5.

286. Guryel E, Pearce R, Rickman M, Bircher M. Thrombo-prophylaxis in pelvic and acetabular trauma patients: a UK consensus? Int Orthop. 2012 Jan;36(1):165-9.

287. Batra S, Kurup H, Gul A, Andrew JG. Thromboprophylaxis following cast immobilisation for lower limb injuries—survey of current practice in United Kingdom. Injury. 2006 Sep;37(9):813-7.

288. Park SJ, Kim CK, Park YS, Moon YW, Lim SJ, Kim SM. Incidence and Factors Predicting Venous Thromboembolism After Surgical Treatment of Fractures Below the Hip. J Orthop Trauma. 2015 Oct;29(10):e349-54.

289. Eisele R, Kinzl L, Koelsch T. Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis. J Bone Joint Surg Am. 2007 May;89(5):1050-6.

290. Horner D, Pandor A, Goodacre S, Clowes M, Hunt BJ. Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilization due to injury: a systematic review. J Thromb Haemost. 2019 Feb; 17(2):329-44.

291. Forsythe RM, Peitzman AB, DeCato T, Rosengart MR, Watson GA, Marshall GT, Ziembicki JA, Billiar TR, Sperry JL. Early lower extremity fracture fixation and the risk of early pulmonary embolus: filter before fixation? J Trauma. 2011 Jun;70(6): 1381-8.

292. Patterson JT, Morshed S. Chemoprophylaxis for Venous Thromboembolism in Operative Treatment of Fractures of the Tibia and Distal Bones: A Systematic Review and Meta-analysis. J Orthop Trauma. 2017 Sep;31(9):453-60.

293. Mangwani J, Sheikh N, Cichero M, Williamson D. What is the evidence for chemical thromboprophylaxis in foot and ankle surgery? Systematic review of the English literature. Foot (Edinb). 2015 Sep;25(3):173-8.

294. Fleischer AE, Abicht BP, Baker JR, Boffeli TJ, Jupiter DC, Schade VL. American College of Foot and Ankle Surgeons' clinical consensus statement: risk, prevention, and diagnosis of venous thromboembolism disease in foot and ankle surgery and injuries requiring immobilization. J Foot Ankle Surg. 2015 May-Jun;54(3):497-507.

295. Metz R, Verleisdonk EJMM, van der Heijden GJMG. Insufficient Evidence for Routine Use of Thromboprophylaxis in Ambulatory Patients with an Isolated Lower Leg Injury Requiring Immobilization: Results of a Meta-Analysis. Eur J Trauma Emerg Surg. 2009 Apr;35(2):169-75.

296. Richey JM, Ritterman Weintraub ML, Schuberth JM. Incidence and Risk Factors of Symptomatic Venous Thromboembolism Following Foot and Ankle Surgery. Foot Ankle Int. 2019 Jan;40(1):98-104.

297. Zheng X, Li DY, Wangyang Y, Zhang XC, Guo KJ, Zhao FC, Pang Y, Chen YX. Effect of Chemical Thromboprophylaxis on the Rate of Venous Thromboembolism After Treatment of Foot and Ankle Fractures. Foot Ankle Int. 2016 Nov;37(11): 1218-24.

298. Saragas NP, Ferrao PNF, Saragas E, Jacobson BF. The impact of risk assessment on the implementation of venous thromboembolism prophylaxis in foot and ankle surgery. Foot Ankle Surg. 2014 Jun;20(2):85-9.

299. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002 Sep 5;347(10):726-30.

300. Braithwaite I, De Ruyter B, Semprini A, Ebmeier S, Kiddle G, Willis N, Carter J, Weatherall M, Beasley R. Cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism. BMJ Open. 2016 Oct 4;6(10):e012764.

301. Blanco JA, Slater G, Mangwani J. A Prospective Cohort Study of Symptomatic Venous Thromboembolic Events in Foot and Ankle Trauma: The Need for Stratification in Thromboprophylaxis? J Foot Ankle Surg. 2018 May - Jun;57(3): 484-8.

302. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

303. Watson U, Hickey BA, Jones HM, Perera A. A critical evaluation of venous thromboembolism risk assessment models used in patients with lower limb cast immobilisation. Foot Ankle Surg. 2016 Sep;22(3):191-5.

304. Douillet D, Nemeth B, Penaloza A, Le Gal G, Moumneh T, Cannegieter SC, Roy PM. Venous thromboembolism risk stratification for patients with lower limb trauma and cast or brace immobilization. PLoS One. 2019 Jun 20;14(6): e0217748.

305. Carr P, Ehredt DJ Jr, Dawoodian A. Prevention of Deep Venous Thromboembolism in Foot and Ankle Surgery. Clin Podiatr Med Surg. 2019 Jan; 36(1):21-35.

306. Warren JA, Sundaram K, Hampton R, Billow D, Patterson B, Piuzzi NS. Venous thromboembolism rates remained unchanged in operative lower extremity orthopaedic trauma patients from 2008 to 2016. Injury. 2019 Oct; 50(10):1620-6.

307. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF; LIFENOX Investigators. Low-molecular-weight heparin and mortality in acutely ill medical patients. N Engl J Med. 2011 Dec 29;365(26):2463-72.

308. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N; Prophylaxis in Medical Patients with Enoxaparin Study Group. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999 Sep 9;341(11):793-800.

309. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. Lancet. 1975 Jul 12;2(7924): 45-51.

310. Millar JA. Effect of medical thromboprophylaxis on mortality from pulmonary embolus and major bleedingy. Australas Med J. 2015 Sep 30;8(9): 286-91.

12 - Should VTE prophylaxis be administered to patients with a hip fracture who do not undergo surgery?

Response/Recommendation: 1. For patients with a non-displaced hip-fracture not requiring surgery, a standard prophylactic regimen of either low-molecular-weight- heparin (LMWH), fondaparinux, low dose unfractionated heparin (LDUFH), adjusted-dose vitamin K antagonist (VKA) or aspirin (ASA) should be considered.

2. For patients with a displaced hip fracture who are treated conservatively, venous thromboembolism (VTE) prophylaxis should be considered in a similar fashion to hip-fracture surgery patients.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.78% Disagree 2.22% Abstain 0.00% (Strong Consensus).

Rationale: Patients who undergo hip-fracture surgery (HFS) are at high-risk for developing post-operative VTE, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Multiple randomized controlled trials (RCT) showed that either LMWH, fondaparinux, LDUFH, adjusted dose VKA, or ASA reduced the occurrence of post-operative VTE.

While the majority of patients with hip fractures receive operative management, certain patients (4 - 8%) with either intracapsular fractures, significant medical morbidities precluding surgery, non-displaced patterns, or with delayed presentation are treated conservatively. For patients with a hip fracture who are treated conservatively no RCT have been performed to investigate whether thromboprophylaxis is effective in preventing symptomatic VTE[311]. However, numerous studies have investigated the *preoperative prevalence* of asymptomatic DVT in patients with a hip fracture.

In 1999, authors from Kings College Hospital United Kingdom (UK) performed a phlebography in hip-fracture patients awaiting surgery, and who were not operated on until after 48 hours following their hospital admission. All patients were treated with 5,000 IU of unfractionated subcutaneous heparin at admission and every 12h thereafter. They found that 13/21 (62%) of patients had an asymptomatic DVT in the affected limb, and 1/21 (4.8%) patient had clinical signs and symptoms of VTE[312].

In another investigation,101 consecutive patients with a hip fracture who received preoperative prophylactic anticoagulation, underwent doppler ultrasound evaluation before surgery. DVT was found in 10/101 (9.9%) patients, and two patients (2%) developed a symptomatic PE. The authors suggested that a delay in surgery resulted in a higher risk of DVT[313].

In another similar study among 208 individuals with a hip fracture, patients underwent indirect multidetector computed tomographic venography for preoperative VTE detection after admission. The prevalence of preoperative asymptomatic VTE was 11.1% (23/208 of patients). While no patients had a symptomatic event, they noted that VTE occurrence correlated with surgical delay[314].

While multiple observational studies confirmed a 10 - 25% prevalence of asymptomatic VTE prior to surgery, no large studies substantiating the rates of symptomatic VTE in non-surgically treated hip fractures have been published yet. Nevertheless, one large study from a single institution in the UK showed that among 5,300 with a proximal femur fracture, 2.2% developed a post-operative symptomatic VTE despite the use of thromboprophylaxis[315].

Considerations: For patients with a hip-fracture who are treated conservatively, the risk of asymptomatic VTE is certainly high and ranges between 10 - 25% in large observational studies. While the risk for symptomatic VTE in hip-fracture patients not receiving surgery remains unknown, smaller studies suggest a rate of 2% which is in line with studies among HFS patients.

Additionally, time until surgery is an important predictor for the occurrence of pre-operative VTE, hence it is expected that for patients with displaced hip fracture (thus those who are bed-confined), the risk for VTE is significant.

Finally, the data on the effectiveness of thromboprophylaxis in patients with a hip fracture not undergoing surgery remains lacking. However, extrapolating from HFS literature, we speculate that the effectiveness of thromboprophylaxis applies to non-surgical patients, as the risks of VTE in this patient population are at least similar, and perhaps greater in patients who are immobilized, or bed confined.

Banne Nemeth, Clifford W. Colwell

References

311. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

312. Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. Injury. 1999 Nov;30(9):605-7.

313. Smith EB, Parvizi J, Purtill JJ. Delayed surgery for patients with femur and hip fractures-risk of deep venous thrombosis. J Trauma. 2011 Jun;70(6):E113-6.

314. Shin WC, Woo SH, Lee SJ, Lee JS, Kim C, Suh KT. Preoperative Prevalence of and Risk Factors for Venous Thromboembolism in Patients with a Hip Fracture: An Indirect Multidetector CT Venography Study. J Bone Joint Surg Am. 2016 Dec 21; 98(24):2089-95.

315. McNamara I, Sharma A, Prevost T, Parker M. Symptomatic venous thromboembolism following a hip fracture. Acta Orthop. 2009 Dec;80(6):687-92.

13 - Is routine VTE prophylaxis needed for patients undergoing osteotomy around the knee?

Response/Recommendation: Routine use of mechanical and/or chemical thromboprophylaxis for patients undergoing osteotomy around the knee is recommended.

Strength of Recommendation: Moderate.

Delegates vote: Agree 93.48% Disagree 2.17% Abstain 4.35% (Strong Consensus).

Rationale: Osteotomies around the knee are used for deformity correction / realignment and is an effective alternative to total knee arthroplasty (TKA) for certain patients with isolated compartment arthritis of the knee. Through osteotomy the mechanical axis is transferred from the arthritic compartment to the adjacent compartment that provides pain relief as well a possible delay in progression of osteoarthritis[316]. There is currently a general consensus about venous thromboembolism (VTE) prophylaxis following TKA[317-319]. However, the treatment of VTE following knee osteotomy has not been well-established although the incidence was relatively high from 2.4 to 41%[320,321]. The rates of deep venous thrombosis (DVT) in the included studies ranged between 0.5% to 25.5%. Sidhu et al., and Giuseffi et al., did not use imaging modalities routinely to check for DVT and reported rates of 0.5% and 1.1%, respectively[322,323]. Kubota et al., and Onishi et al., performed ultrasonography one week post-operatively and found DVT rates several times higher, with rates of 25.5% and 13.8%, respectively[324,325]. Kobayashi et al., performed a randomized

TABLE I Descriptive and rates of VTE in the included studies.

Study year (Type)	Number of knees	VTE prophylaxis	Follow up	Demographics	DVT rate	PE rate	Stroke rate	Myocardial infarction rate	Mortality from thromboembolic event	Significant bleeding events
Sidhu et al.[322] 2020 (Observational)	200	None unless risk factors in which aspirin prescribed	Minimum 2 years follow up	Mean age: 52.6 years Sex: 143 males Mean BMI 31.7 11 smokers	1 case (0.5%). Resolved with anticoagulants.	1 (0.5%)	0	0	0	0
Kubota et al.[324] 2021 (Observational)	137	None preop. One case prasugurel, aspirin, sarpogrelate and ethyl icospenatate. Post op edoxaban for 2 weeks	1 weeks. US performed in all cases	Mean age: 62.1 Sex: 37 males Mean BMI 26.2 Smokers: N/A	35 (25.5%). No symptomatic DVT and all in soleus vein.	0	0	0	0	0
Giuseffi et al.[323] 2015 (Observational)	89	Not stated	Mean: 4 years	Mean age: 48.1 Sex: 64 males Mean BMI: N/A Smokers: 17	2 (2.2%) 1 of the above required vascular surgery in the popliteal artery.	1 (1.1%)	0	0	0	0
Onishi et al.[325] 2020 (Observational)	326	Postop elastic compression stockings and mechanical compression devices. All patients had edoxaban for one week	US performed 1 month before and 7 days after surgery	Mean age: 61.7 Sex: 151 males Mean BMI: 25.2 Smokers: 17	45 (13.8%)	0	0	0	0	0
Kobayashi et al.[326] 2017 (RCT)	135 66 edoxaban group 69 non edoxaban group	All had elastic stockings and foot pump. Edoxaban 15/30mg for 14 days. Non edoxaban group had no chemical propylaxis	Angiography performed on day 7 post op	Mean age: 66 Sex: 45 males Mean BMI: 25.6 Smokers: 17	11 (16.7%) in edoxaban group 15 (21.7%) in non edoxaban group	4 (6%) in edoxaban group 11 (15.9%) in non edoxaban group	0	0	0	0

VTE = Venous thromboembolism; DVT = Deep venous thrombosis; PE = Pulmonary embolism; BMI = Body mass index; US = Ultrasound.

controlled trial investigating DVT rates via venography following tibial osteotomy. The edoxaban (a factor Xa inhibitor) treated group had a rate of 16.7% compared to the non-edoxaban rate of 21.7%[326]. The incidence of pulmonary embolism (PE), as reported in three of the five studies. Sidhu et al., report a rate of 0.5%, Giuseffi et al., a rate of 1.1% and Kobayashi et al., reported PE rate of 6.3% in the edoxaban group and 16.7% in the non-edoxaban group[322,323,326]. None of the studies reported any VTE related complications such as death, bleeding, or others.

There is scant literature related to the subject of VTE after knee osteotomy (Table I). Based on the available data, however, it likely that these patients are at increased risk of DVT and some form of thromboprophylaxis may need to be administered to these patients. Combined with extrapolation from the data from TKA literature, we believe that mechanical and/or chemoprophylaxis (including aspirin) should be effective in these patients.

Yasushi Oshima, Hasan R. Mohammad, Tokifumi Majima, Hemant G. Pandit

References

316. Sabzevari S, Ebrahimpour A, Roudi MK, Kachooei AR. High Tibial Osteotomy: A Systematic Review and Current Concept. Arch Bone Jt Surg. 2016 Jun;4(3):204-12.

317. Bala A, Huddleston JI 3rd, Goodman SB, Maloney WJ, Amanatullah DF. Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors? Clin Orthop Relat Res. 2017 Sep;475(9):2205-13.

318. Tateiwa T, Ishida T, Masaoka T, Shishido T, Takahashi Y, Onozuka A, Nishida J, Yamamoto K. Clinical course of asymptomatic deep vein thrombosis after total knee arthroplasty in Japanese patients. J Orthop Surg (Hong Kong). 2019 May-Aug;27(2):2309499019848095.

319. Zeng Y, Si H, Wu Y, Yang J, Zhou Z, Kang P, Pei F, Shen B. The incidence of symptomatic in-hospital VTEs in Asian patients undergoing joint arthroplasty was low: a prospective, multicenter, 17,660-patient-enrolled cohort study. Knee Surg Sports Traumatol Arthrosc. 2019 Apr;27(4):1075-82.

320. Martin R, Birmingham TB, Willits K, Litchfield R, Lebel ME, Giffin JR. Adverse event rates and classifications in medial opening wedge high tibial osteotomy. Am J Sports Med. 2014 May;42(5):1118-26.

321. Miller BS, Downie B, McDonough EB, Wojtys EM. Complications after medial opening wedge high tibial osteotomy. Arthroscopy. 2009 Jun;25(6):639-46.

322. Sidhu R, Moatshe G, Firth A, Litchfield R, Getgood A. Low rates of serious complications but high rates of hardware removal after high tibial osteotomy with Tomofix locking plate. Knee Surg Sports Traumatol Arthrosc. 2021 Oct;29(10): 3361-7.

323. Giuseffi SA, Replogle WH, Shelton WR. Opening-Wedge High Tibial Osteotomy: Review of 100 Consecutive Cases. Arthroscopy. 2015 Nov;31(11):2128-37.

324. Kubota M, Kim Y, Inui T, Sato T, Kaneko H, Ishijima M. Risk factor for venous thromboembolism after high tibial osteotomy -analysis of patient demographics, medical comorbidities, operative valuables, and clinical results. J Orthop. 2021 May 4;25:124-8.

325. Onishi S, Iseki T, Kanto R, Kanto M, Kambara S, Yoshiya S, Tachibana T, Nakayama H. Incidence of and risk factors for deep vein thrombosis in patients undergoing osteotomies around the knee: comparative analysis of different osteotomy types. Knee Surg Sports Traumatol Arthrosc. 2021 Oct;29(10): 3488-94.

326. Kobayashi H, Akamatsu Y, Kumagai K, Kusayama Y, Ishigatsubo R, Mitsuhashi S, Kobayashi A, Aratake M, Saito T. The use of factor Xa inhibitors following opening-wedge high tibial osteotomy for venous thromboembolism prophylaxis. Knee Surg Sports Traumatol Arthrosc. 2017 Sep;25(9):2929-35.

14 - Is routine VTE prophylaxis required for patients with isolated patellar fracture who may or may not require surgery?

Response/Recommendation: Routine thromboprophylaxis is not indicated for patients with isolated patellar fracture but should be considered for patients with risk factors for venous thromboembolism (VTE).

Strength of Recommendation: Limited.

Delegates vote: Agree 93.02% Disagree 6.98% Abstain 0.00% (Strong Consensus).

Rationale: Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a serious complication that occurs in 1.6 - 21% of patients with lower extremity fractures[327-330]. However, there is limited data regarding the incidence of VTE in patients with isolated patellar fractures, and the use of routine VTE prophylaxis is controversial. Tan et al.[331], conducted a retrospective review of 716 patients admitted to a single institution to investigate the incidence and location of postoperative DVT in patients who underwent operative repair of isolated patella fractures. Duplex ultrasound (DUS) was used for diagnosis only in patients clinically suspected of DVT. All patients received subcutaneous low-molecular-weight heparin (LMWH) and sequential compression devices (SCD) throughout admission as part of routine VTE prophylaxis. Of the 716 patients, 29 cases were diagnosed with postoperative DVT, with an incidence of 4.1%. The majority of the diagnosed DVT were located distally (n = 22; 3.1%), while 0.98% (n = 7) were located proximally (i.e., localized in the popliteal vein or proximally). There were no cases of PE. Tan et al.[332], conducted a similar study investigating preoperative DVT in patients with isolated patellar fractures using nearly identical methodology. However, this study differed in that all participants underwent DUS of bilateral lower extremities at admission and then every three days until discharge. Of the 790 included patients, 35 developed a preoperative DVT (4.4%), with 3.2% (n = 25) located distally and 1.2% (n = 10) located proximally. No DVT were found on admission. The authors recommend individualized risk stratification and early anticoagulation for patients with risk factors (age ≥ 65 years, D-dimer > 0.5 mg/L and albumin < 35 g/L). Similarly, Wang et al.[333], conducted a retrospective analysis of the perioperative incidence and location of DVT following isolated lower extremity fractures in patients that received routine thromboprophylaxis and DVT monitoring with DUS. A small cohort of 59 patients with isolated patellar fractures were included in the study. Overall, 15 (25.4%) patients in the patellar cohort developed a DVT. One patient had a proximal DVT (1.7%), while the remaining DVT were distal (23.7%). No patients with patellar fracture developed symptomatic PE. The authors concluded that the perioperative incidence of DVT is high following isolated lower extremity fractures, although the majority were distal DVT, and the rate of symptomatic PE was low.

Only one study has assessed the rate of VTE in patellar fracture patients who did not receive any thromboprophylaxis. Selby et al., conducted a multicenter prospective study in a population of patients with a variety of isolated lower extremity fractures including fractures of the tibia, fibula, ankle, patella and foot[334]. Fractures treated both operatively and conservatively were included, and 82% of the patients were treated in a cast or splint for an average of 42 days. All patients were followed with a telephone interview at two, six, and twelve weeks to determine the prevalence of symptomatic VTE. Suspected DVT and PE were investigated in a standardized manner using DUS and computed tomography (CT) pulmonary angiography. Overall, 1,200 patients were enrolled, of which 60 patients (5%) had patella fractures. In total, there were seven confirmed VTE events (0.6%), including two proximal DVT (0.17%), three distal calf DVT (0.25%), and two PE (0.17%). There were no fatal PE. The overall event rates were too low to allow multivariate analyses for predictors of VTE. Since a breakdown of VTE by fracture location was not reported, the true incidence of VTE in the patients with isolated patella fractures was unclear.

Additionally, several large database studies have investigated the incidence of VTE following operatively treated isolated patellar fracture in populations that included both patients who received routine prophylaxis and patients who did not. Warren et al., used the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to evaluate the annual incidence of 30-day thrombotic events for a variety of isolated lower extremity fractures from 2008 to 2016[327]. Overall, 2,825 patients with operatively managed patellar fracture were identified. The VTE rate in this cohort was 0.9% (n = 26), including 18 DVT (0.6%) and 11 PE (0.4%). The authors concluded that the VTE rates from 2008 to 2016 have remained relatively unchanged and that thromboembolic guidelines should be reassessed. Likewise, Kapilow et al.[335], also published a retrospective review using NSQIP that reported the early outcomes after surgical management of isolated patellar fractures in a population of

1,721 patients 65 years of age or older. Overall, only 13 (0.8%) of these patients developed VTE, but the authors noted that this patient cohort was at higher risk for prolonged hospitalization, discharge to a facility, unplanned readmission or reoperation, and surgical site complications in the first 30 days.

Overall, the studies that utilized routine thromboprophylaxis in all patients found the incidence of DVT after isolated patellar fracture to range from 4.1% to 25.4%, with no recorded instances of PE in any of the studies[331-333]. The wide range in the reported incidence of DVT was influenced by the different methodologies used in these studies. For example, the paper by Tan et al.[331], which reported the lowest rate of VTE (4.1%), only scanned symptomatic patients and did not include intermuscular vein blood clots when calculating the incidence of DVT. Conversely, Wang et al.[333], routinely screened all patients using DUS and included intramuscular vein blood clots, which resulted in the highest reported incidence of VTE (25.4%). Notably, if the study by Wang et al.[333], is excluded, the highest reported incidence of DVT drops from 25.4% to 4.4%. This highlights the major discrepancy between studies using different clinical endpoints and VTE screening protocols.

The large cohort studies utilizing the NSQIP database did not control for the routine use of VTE prophylaxis; however, much lower rates of VTE between 0.8 - 0.9% were noted[327,335]. Unfortunately, the NSQIP database does not include VTE prophylaxis, so it is unclear if a prophylaxis was utilized, and if so, what specific type of VTE prophylaxis was used. They also included the largest sample size of any of the included studies, and were the only studies not limited to a single institution, lending increased power and generalizability to their findings.

In all studies, distal DVT was more common than proximal DVT. It is widely accepted that proximal DVT represents a greater risk for the development of PE and requires further treatment, while the clinical relevance of distal DVT remains uncertain and the risk of proximal propagation is not well defined[333,334]. The treatment of distal DVTs is not standardized and may be either monitored with serial scans or actively treated with anticoagulation. The rate of proximal DVT reported in these studies was low, ranging from 0.17% to 1.2%[331-333]. The observed rate of PE was even lower, ranging from 0% to 0.4%[327,331-334]. While the rate of VTE were very low, many studies on isolated patella fractures utilized routine VTE prophylaxis and there were no studies in the literature in which VTE prophylaxis was randomized. As such, the recommendation to routinely use or omit VTE prophylaxis remains difficult to assess. Despite the various methodologies utilized in the reviewed studies, the universally low rate of proximal DVT and PE should be considered in the decision to implement routine VTE prophylaxis in patients with isolated patellar fractures. It may be safer and more cost-effective to initiate VTE prophylaxis only in patients with risk factors for VTE, such as elderly patients, those with longer length of stays, longer operative time, or arrhythmia[331,332]. However, given the limitations of the available data, future studies comparing the use of VTE prophylaxis versus no prophylaxis in patients with isolated patellar fracture are required.

Kara M. McConaghy, Geoffrey H. Westrich, Nicolas S. Piuzzi

References

327. Warren JA, Sundaram K, Hampton R, Billow D, Patterson B, Piuzzi NS. Venous thromboembolism rates remained unchanged in operative lower extremity orthopaedic trauma patients from 2008 to 2016. Injury. 2019 Oct; 50(10):1620-6.

328. Lapidus LJ, Ponzer S, Pettersson H, de Bri E. Symptomatic venous thromboembolism and mortality in orthopaedic surgery - an observational study of 45 968 consecutive procedures. BMC Musculoskelet Disord. 2013 Jun 4;14:177.

329. Park SJ, Kim CK, Park YS, Moon YW, Lim SJ, Kim SM. Incidence and Factors Predicting Venous Thromboembolism After Surgical Treatment of Fractures Below the Hip. J Orthop Trauma. 2015 Oct;29(10):e349-54.

330. Tan L, Qi B, Yu T, Wang C. Incidence and risk factors for venous thromboembolism following surgical treatment of fractures below the hip: a meta-analysis. Int Wound J. 2016 Dec;13(6):1359-71.

331. Tan Z, Hu H, Deng X, Zhu J, Zhu Y, Ye D, Cheng X, Zhang Y. Incidence and risk factors for deep venous thrombosis of lower extremity after surgical treatment of isolated patella fractures. J Orthop Surg Res. 2021 Jan 28;16(1):90.

332. Tan Z, Hu H, Wang Z, Wang Y, Zhang Y. Prevalence and risk factors of preoperative deep venous thrombosis in closed patella fracture: a prospective cohort study. J Orthop Surg Res. 2021 Jun 23;16(1):404.

333. Wang H, Kandemir U, Liu P, Zhang H, Wang PF, Zhang BF, Shang K, Fu YH, Ke C, Zhuang Y, Wei X, Li Z, Zhang K. Perioperative incidence and locations of deep vein thrombosis following specific isolated lower extremity fractures. Injury. 2018 Jul; 49(7):1353-7.

334. Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F. Symptomatic venous thromboembolism uncommon without thromboprophylaxis after isolated lower-limb fracture: the knee-to-ankle fracture (KAF) cohort study. J Bone Joint Surg Am. 2014 May 21;96(10):e83.

335. Kapilow J, Ahn J, Gallaway K, Sorich M. Early Outcomes After Surgical Management of Geriatric Patella Fractures. Geriatr Orthop Surg Rehabil. 2021 Jan 24;12:2151459320987699.

15 - Does WALANT for tibia/fibula fracture fixation have an increased risk of VTE events?

Response/Recommendation: Whether wide-awake local anesthesia no tourniquet (WALANT) for tibia/fibula fracture fixation has a risk of venous thromboembolism (VTE) compared to other techniques for tibia/fibula fracture is unknown. We recommend using anticoagulant prophylaxis as per existing thromboprophylaxis guidelines, independent of the technique used.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.35% Disagree 4.65% Abstain 0.00% (Strong Consensus).

Rationale: WALANT is a surgical technique that was first described by Dr. Donald H. Lalonde for surgery of the wrist and hand[336]. To perform the technique, the surgeon injects a lidocaine and epinephrine mixture into the operative site. The lidocaine provides surgical anesthesia and allows the patient to remain comfortably awake during the procedure. The epinephrine assists in hemostasis and eliminates the need for a tourniquet[336]. Aside from wrist and hand surgery, WALANT has been successfully used for plate fixation of distal radius fractures[337] and clavicular fractures[338]. The successful application of WALANT for upper extremity fracture repair has prompted investigations in its utility for lower extremity fractures.

The literature on WALANT for lower extremity fractures is limited. We identified a case report, published as an abstract from a scientific meeting describing the use of WALANT in a patient that underwent plating of a proximal tibia fracture. The authors did not report any complications[339]. Li et al., described a prospective case series of 13 patients using WALANT for malleolar fractures and no complications, including VTE, were reported[340]. Bilgetekin et al., performed a retrospective chart review of 31 patients that underwent WALANT for foot and ankle surgery[341]. Of these patients, 20 had malleolar fractures and no complications, including VTE, were reported. Poggetti et al., studied the use of WALANT for removal of distal fibula implants[342]. In their study, 60 patients were scheduled for distal fibula hardware removal following open reduction internal fixation and were randomized to receive either WALANT or a stimulation guided sciatic and femoral nerve block with tourniquet. The primary outcome was not defined, and like the previous studies, no VTE were reported[342].

Overall, these studies are limited by their small size, heterogeneity, and lack of power to detect VTE complications. As a result, the risk of VTE in patients receiving WALANT for tibia/fibula fracture fixation remains poorly defined and we are unable to recommend a specific anticoagulant regimen for thromboprophylaxis.

Thomas Volk, Jeffrey J. Mojica, Azlina A. Abbas

References

336. Lalonde D, Martin A. Epinephrine in local anesthesia in finger and hand surgery: the case for wide-awake anesthesia. J Am Acad Orthop Surg. 2013 Aug; 21(8):443-7.

337. Huang YC, Hsu CJ, Renn JH, Lin KC, Yang SW, Tarng YW, Chang WN, Chen CY. WALANT for distal radius fracture: open reduction with plating fixation via wide-awake local anesthesia with no tourniquet. J Orthop Surg Res. 2018 Aug 6; 13(1):195.

338. Ahmad AA, Ubaidah Mustapa Kamal MA, Ruslan SR, Abdullah S, Ahmad AR. Plating of clavicle fracture using the wide-awake technique. J Shoulder Elbow Surg. 2020 Nov;29(11):2319-25.

339. Shamsudin Z, Ahmad AA, Ahmad AR. Patella Fracture Fixation Via Wide Awake Local Anesthesia No Tourniquet (Walant) Technique. Orthop J Sports Med. 2020; 8(5_suppl5):2325967120S00087.

340. Li YS, Chen CY, Lin KC, Tarng YW, Hsu CJ, Chang WN. Open reduction and internal fixation of ankle fracture using wide-awake local anaesthesia no tourniquet technique. Injury. 2019 Apr;50(4):990-4.

341. Bilgetekin YG, Kuzucu Y, Öztürk A, Yüksel S, Atilla HA, Ersan Ö. The use of the wide-awake local anesthesia no tourniquet technique in foot and ankle injuries. Foot Ankle Surg. 2021 Jul;27(5):535-8.

342. Poggetti A, Del Chiaro A, Nicastro M, Parchi P, Piolanti N, Scaglione M. A local anesthesia without tourniquet for distal fibula hardware removal after open reduction and internal fixation: the safe use of epinephrine in the foot. A randomized clinical study. J Biol Regul Homeost Agents. 2018 Nov-Dec; 32(6)(Suppl. 1):57-63.

16 - Should patients undergoing hardware removal of lower extremity require routine VTE prophylaxis?

Response/Recommendation: Patients undergoing removal of hardware from lower extremity are at low risk of venous thromboembolism (VTE). Thus, routine VTE thromboprophylaxis is not recommended.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.56% Disagree 2.22% Abstain 2.22% (Strong Consensus).

Rationale: VTE affects thousands of people in the world each year and lower limb surgery is a known acquired risk factor[343] However, there is a paucity of evidence relating to thromboembolism after lower extremity hardware removed.

Systematic review of the literature, using the search terms appended below, revealed no studies that directly address thromboembolic complications or thromboprophylaxis around lower extremity hardware removal. Fenelon et al., performed a 10-year retrospective review of complications following 1,482 ankle open reduction internal fixation (ORIF) cases, and identified no deep venous thrombosis (DVT) or pulmonary embolism (PE) in the 185 (12.5%) cases who underwent hardware removal during the follow-up period; however, the use of thromboprophylaxis was not reported[344]. Kovar et al., published a 16-year descriptive outcomes study examining complications following implant removal in proximal femur fractures, and reported that none of the 61 complications seen in the 428 procedures examined were DVT or PE; however, there was no mention of whether or not thromboprophylaxis was implemented[345].

Clinical practice guidelines published by the American Academy of Orthopaedic Surgeons (AAOS)[346], the American College of Chest Physicians (ACCP)[347], and the American College of Foot and Ankle Surgeons (ACFAS)[348] do not specifically address hardware removal. The National Institute for Health and Care Excellence (NICE) guidelines[349] recommend anticoagulation following foot and ankle surgery if prolonged immobilization if expected, or surgical time is greater than 90 minutes, or when the risk of VTE development outweighs the risk of bleeding[350]. These recommendations could be extrapolated to cases of lower extremity hardware removal although they are not specifically intended for this setting.

Knowledge of Virchow's triad (hypercoagulability, endothelial injury and venous stasis) and the mechanisms of production of thromboembolic disease, can help guide thromboprophylaxis in individual situations where there is no specific evidence[351]. Hardware removal could be stratified as complicated or not with respect to the difficulty of removal, surgical time, bony manipulation, use of tourniquet, and need for general anesthesia. Although this may seem logical, there is currently no evidence to support this practice.

Clinicians can combine guideline recommendations for other patient groups with individual patient VTE risk factors[352,353]. The Caprini score, while not specifically validated in this setting, may be used to guide decisions about VTE prophylaxis[353]. The Caprini score has been validated in over 100 trials worldwide involving more than 250.000 patients[354]. It has specific items for orthopaedic surgery, but hardware removal has again not been independently assessed.

In conclusion, we have no evidence that lower extremity hardware removal independently increases the risk of VTE over a patient's own risk factors. There are no guidelines or evidence for this specific surgical process. For this reason, we recommend a comprehensive assessment of risk factors should

be performed to aid in the decision-making process. If sufficient risk factors are present, mechanical and/or chemical thromboprophylaxis should be considered and weighed against the potential risks of prophylaxis. However, exactly what constitutes sufficient risk remains unknown, especially in this setting of lower extremity hardware removal. Further studies on this topic are needed to develop more specific and evidence-based recommendations.

Karan Goswami, Tomas Roca-Sanchez, Nestor Moreno-Moreu

References

343. Samama CM, Laporte S, Rosencher N, Girard P, Llau J, Mouret P, Fisher W, Martínez-Martín J, Duverger D, Deygas B, Presles E, Cucherat M, Mismetti P; PRONOMOS Investigators. Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery. N Engl J Med. 2020 May 14;382(20):1916-25.

344. Fenelon C, Murphy EP, Galbraith JG, Kearns SR. The burden of hardware removal in ankle fractures: How common is it, why do we do it and what is the cost? A ten-year review. Foot Ankle Surg. 2019 Aug;25(4):546-9.

345. Kovar FM, Strasser E, Jaindl M, Endler G, Oberleitner G. Complications following implant removal in patients with proximal femur fractures - an observational study over 16 years. Orthop Traumatol Surg Res. 2015 Nov;101(7): 785-9.

346. Jacobs JJ, Mont MA, Bozic KJ, Della Valle CJ, Goodman SB, Lewis CG, Yates AC Jr, Boggio LN, Watters WC 3rd, Turkelson CM, Wies JL, Sluka P, Hitchcock K. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Bone Joint Surg Am. 2012 Apr 18;94(8):746-7.

347. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

348. Fleischer AE, Abicht BP, Baker JR, Boffeli TJ, Jupiter DC, Schade VL. American College of Foot and Ankle Surgeons' clinical consensus statement: risk, prevention, and diagnosis of venous thromboembolism disease in foot and ankle surgery and injuries requiring immobilization. J Foot Ankle Surg. 2015 May-Jun; 54(3):497-507.

349. National Guideline Centre (UK). Venous Thromboembolism in over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism. National Institute for Health and Care Excellence (UK); 2018. Accessed August 5, 2021. http://www.ncbi.nlm.nih.gov/books/NBK493720/

350. Carr P, Ehredt DJ Jr, Dawoodian A. Prevention of Deep Venous Thromboembolism in Foot and Ankle Surgery. Clin Podiatr Med Surg. 2019 Jan; 36(1):21-35.

351. Özcan M, Erem M, Turan FN. Symptomatic Deep Vein Thrombosis Following Elective Knee Arthroscopy Over the Age of 40. Clin Appl Thromb Hemost. 2019 Jan-Dec;25:1076029619852167.

352. Sloan M, Sheth N, Lee GC. Is Obesity Associated With Increased Risk of Deep Vein Thrombosis or Pulmonary Embolism After Hip and Knee Arthroplasty? A Large Database Study. Clin Orthop Relat Res. 2019 Mar;477(3):523-32.

353. Golemi I, Salazar Adum JP, Tafur A, Caprini J. Venous thromboembolism prophylaxis using the Caprini score. Dis Mon. 2019 Aug;65(8):249-98.

354. Cronin M, Dengler N, Krauss ES, Segal A, Wei N, Daly M, Mota F, Caprini JA. Completion of the Updated Caprini Risk Assessment Model (2013 Version). Clin Appl Thromb Hemost. 2019 Jan-Dec;25: 1076029619838052.

17 - Should patients undergoing hardware removal of upper extremity require routine VTE prophylaxis?

Response/Recommendation: Patients undergoing removal of hardware from the upper extremity are at extreme low risk of venous thromboembolism (VTE). Thus, routine use of VTE prophylaxis in these patients is not required. The use of aspirin as a VTE prophylaxis may be considered for those at high risk of VTE.

Strength of Recommendation: Consensus.

Delegates vote: Agree 97.78% Disagree 2.22% Abstain 0.00% (Strong Consensus).

Rationale: Although upper extremity deep venous thromboses (UEDVT) is a rare complication after upper extremity surgery, it can have serious consequences[355]. During the past decade, some studies have reported an increased risk of UEDVT in patients undergoing elective orthopaedic procedures of the upper extremity[356,357]. This finding has generated questions regarding the role of prophylactic agents for patients undergoing elective upper extremity surgery. Several studies demonstrate that upper limb surgery can be associated with thrombosis in the upper and lower limbs[358]. Basat et al[359], documented a case report of deep venous thrombosis (DVT) of brachial vein that lead to massive pulmonary thromboembolism after surgical treatment of an ulnar pseudoarthrosis 4 months after prior internal fixation. The surgery lasted 110 minutes including 85 minutes under tourniquet. They suggested the use of a low molecular weight heparin prophylaxis after upper extremity surgeries necessitating long-term immobilization. However, the operation also included autologous iliac crest bone graft harvesting. Many case studies reported on UEDVT events after conservative treatment of clavicular fracture[360-363] and humeral shaft fracture and[364]. Pearsall et al.[365], reported a case of internal jugular vein thrombosis after a case of humerus nonunion treatment including metal removal, iliac bone graft and replating of the humerus shaft.

Importantly, the reported cases confirm that upper and lower extremity DVT can occur in relation to upper limb surgery. However, these studies do not provide any evidence that upper limb surgery confers any additional risk of thromboembolism to the patient over that resulting from individual patient related factors. These events cause symptoms for a relatively small number of patients, but rates of asymptomatic disease may be higher. As yet, the true extent of this as a problem is undefined, which makes risk assessment and management difficult.

The risk of complications following a UEDVT, including post-thrombotic syndrome and pulmonary embolism (PE), is substantially higher compared with a DVT of the lower extremity[355,366]. Risk factors for UEDVT include malignancy, age older than 60 years, dehydration, known thrombophilia, obesity, history of DVT, oral contraceptive or hormonal therapy, varicose veins with phlebitis, multiple comorbidities, and pregnancy[367-369]. Further, Hastie et al., assessed the VTE incidence in 3,357 upper limb procedures and found that the most striking common factor in the patients who sustained UEVTE events was the strong family or personal history of DVT, or PE[357].

Surgery resulting in reduced mobility is a recognized risk factor for VTE[370]. The exact degree to which mobility needs to be reduced has not been established, although one study found reduced mobility for 3 days or more was associated with an increased risk of symptomatic lower limb DVT[371]. Recently, Lv et al.[372], reported a case of PE after an external and internal

fixation procedure of distal radius and ulna with DVT in bilateral posterior tibial veins. However, the procedure was prolonged (4 hours), an iliac graft was harvested, and they described that the patient was reluctant to move out of bed for 3 days because of pain. Although the majority of the cases of hardware removal from upper limb might seems straight forward with low risk of complications, in certain situations the removal procedures can become challenging. Certain factors such as prolonged surgical time, excessive bone manipulation, and the use of tourniquet can put patients at higher risk of complications after surgery[373].

There is no consensus regarding the role and efficacy of prophylactic measures in preventing UEDVT after hardware removal surgery. In general, the existing guidance for VTE prophylaxis for elective upper limb surgery is unclear, and contradicting recommendations are unhelpful.

The American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP)[374] do not offer specific guidelines regarding the use of prophylactic agents after elective orthopaedic procedures of the upper extremity. Guidelines from the United Kingdom National Institute for Clinical Excellence (NICE)[368] recommend VTE prophylaxis in major orthopaedic procedures and interpret this as hip and knee arthroplasty surgeries and upper limb surgery lasting longer than 90 minutes. The Scottish Intercollegiate Guidelines Network (SIGN) VTE guidelines recommended that this should include the total procedure time, including the time to administer an anesthetic[375]. There is no evidence for the specific timings chosen, and for this reason, separate guidelines produced by SIGN refer only to "prolonged immobility" associated with orthopaedic procedures or plaster immobilization.

The existing guidelines are consistent in that they recommend an assessment of risk for each patient. This must be the standard of care and should form part of the consent process during which the risk of bleeding and VTE are considered[358]. In addition, it is recommended that mechanical prophylaxis (including fitted compression hosiery, intermittent pneumatic compression devices, and foot pumps) be routinely offered to patients undergoing elective upper limb surgery on admission and continued until discharge, unless there is a specific contraindication[374]. Chemical prophylaxis (e.g., aspirin, unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], factor Xa inhibitors, thrombin inhibitors or warfarin) can be considered when patients are judged to have an increased VTE risk on the basis of their individual patient-related factors balanced against the risk of bleeding[358]. However, there is likely no need for chemical prophylaxis if such patients are able to quickly return to their prior level of mobility. For those who cannot, chemical prophylaxis is suggested with no recommendation regarding length of use after surgery[358]. With all forms of chemical prophylaxis, the risk of bleeding must be weighed carefully before beginning therapy. No evidence exists regarding the length of use; however, the authors recommend at least 2 weeks if chemical prophylaxis is given because the risk of DVT is highest in the first 2 weeks following surgery.

In conclusion, there is no evidence to suggest that elective hardware removal from the upper limb confers an additional VTE risk in itself. The quality of this evidence is poor, and further research should be undertaken to examine the extent of the problem and any specific risks associated with these procedures. Due to the paucity of studies evaluating the efficacy of prophylaxis for UEDVT after implant removal, specific recommendations cannot be made regarding the choice of VTE prophylaxis and the length of use after these surgeries. It seems reasonable to adopt a multimodal approach that involves all patients receiving mechanical prophylaxis, with chemical prophylaxis reserved for those who are at high risk for VTE.

Mohammad S. Abdelaal, Nestor Moreno Moreu

References

355. Sindhu KK, Cohen B, Blood T, Gil JA, Owens B. Upper Extremity Deep Venous Thrombosis Prophylaxis After Elective Upper Extremity Surgery. Orthopedics. 2018 Jan 1;41(1):21-7.

356. Dattani R, Smith CD, Patel VR. The venous thromboembolic complications of shoulder and elbow surgery: a systematic review. Bone Joint J. 2013 Jan;95-B(1):70-4.

357. Hastie GR, Pederson A, Redfern D. Venous thromboembolism incidence in upper limb orthopedic surgery: do these procedures increase venous thromboembolism risk? J Shoulder Elbow Surg. 2014 Oct;23(10):1481-4.

358. Anakwe RE, Middleton SD, Beresford-Cleary N, McEachan JE, Talwalkar SC. Preventing venous thromboembolism in elective upper limb surgery. J Shoulder Elbow Surg. 2013 Mar;22(3):432-8.

359. Basat HC, Kalem M, Binnet MS, Demirtaş M. Pulmonary thromboembolism after surgical treatment of ulnar pseudoarthrosis: a case report. Acta Orthop Traumatol Turc. 2011;45(4):284-7.

360. Jones RE, McCann PA, Clark DA, Sarangi P. Upper limb deep vein thrombosis: a potentially fatal complication of a clavicle fracture. Ann R Coll Surg Engl. 2010 Jul; 92(5):W36-8.

361. Peivandi MT, Nazemian Z. Clavicular fracture and upper-extremity deep venous thrombosis. Orthopedics. 2011 Mar 11;34(3):227.

362. Ranke H, Märdian S, Haas NP, Baecker H. [Thrombosis of the subclavian vein after conservative treatment of a clavicular fracture: A rare complication]. Unfallchirurg. 2016 Mar;119(3):255-8.

363. Adla DN, Ali A, Shahane SA. Upper-extremity deep-vein thrombosis following a clavicular fracture. Eur J Orthop Surg Traumatol. 2004 Sep;14(3):177-9.

364. Sawyer GA, Hayda R. Upper-extremity deep venous thrombosis following humeral shaft fracture. Orthopedics. 2011 Jan 1;34(2):141.

365. Pearsall AW 4th, Stokes DA, Russell GV Jr. Internal jugular deep venous thrombosis after surgical treatment of a humeral nonunion: a case report and review of the literature. J Shoulder Elbow Surg. 2004 Jul-Aug;13(4):459-62.

366. Spaniolas K, Velmahos GC, Wicky S, Nussbaumer K, Petrovick L, Gervasini A, De Moya M, Alam HB. Is upper extremity deep venous thrombosis underdiagnosed in trauma patients? Am Surg. 2008 Feb;74(2):124-8.

367. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Old and new risk factors for upper extremity deep venous thrombosis. J Thromb Haemost. 2005 Nov;3(11):2471-8.

368. Venous thromboembolism: reducing the risk for patients in hospital | Guidance | NICE. Accessed June 27, 2021. https://www.nice.org.uk/guidance/cg92

369. Whiting PS, White-Dzuro GA, Greenberg SE, VanHouten JP, Avilucea FR, Obremskey WT, Sethi MK. Risk Factors for Deep Venous Thrombosis Following Orthopaedic Trauma Surgery: An Analysis of 56,000 patients. Arch Trauma Res. 2016 Jan 23;5(1):e32915.

370. Bosson JL, Pouchain D, Bergmann JF; ETAPE Study Group. A prospective observational study of a cohort of outpatients with an acute medical event and reduced mobility: incidence of symptomatic thromboembolism and description of thromboprophylaxis practices. J Intern Med. 2006 Aug;260(2):168-76.

371. Motykie GD, Caprini JA, Arcelus JI, Zebala LP, Lee CE, Finke NM, Tamhane A, Reyna JJ. Risk factor assessment in the management of patients with suspected deep venous thrombosis. Int Angiol. 2000 Mar;19(1):47-51.

372. Lv B, Xue F, Shen YC, Hu FB, Pan MM. Pulmonary thromboembolism after distal ulna and radius fractures surgery: A case report and a literature review. World J Clin Cases. 2021 Jan 6;9(1):197-203.

373. McLendon K, Goyal A, Bansal P, Attia M. Deep Venous Thrombosis Risk Factors. In: StatPearls. StatPearls Publishing; 2021.

374. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2)(Suppl):e278S-325S.

375. Prevention and management of venous thromboembolism. SIGN. Accessed June 28, 2021. https://testing36.scot.nhs.uk

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G856).

NOTE: The ICM-VTE Trauma Delegates includes Jaimo Ahn, MD, PhD, University of Michigan, Ann Arbor, Michigan; Azlina A. Abbas, MD, University of Malaya, Kuala Lumpur, Malaysia; Mohammad S. Abdelaal, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Ahmed A. Alabdali, MD, Orthopedic Complex Trauma Fellow, King Saud University, Riyadh, Saudi Arabia; Abdulaziz N. Aljurayyan, MD, College of Medicine, King Saud University, Riyadh, Saudi Arabia; Abtin Alvand, MD, University of Oxford, Oxford, United Kingdom; Guillermo Araujo, MD, Universidad Nacional San Marcos, Lima, Peru; Antonio Benjumea-Carrasco, MD, Universidad Complutense de Madrid, Madrid, Spain; Svetlana A. Bozhkova, MD, Vreden National Medical Research Center of Traumatology and Orthopedics, St. Petersburg, Russia; Malin S. Carling, MD, Department of Orthopedics, Sahlgrenska University Hospital, Gothenburg, Sweden; Francisco Chana-Rodríguez, MD, PhD, General University Hospital Gregorio Marañón, Madrid, Spain; Emanuele Chisari, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Clifford W. Colwell, MD, Scripps Green Hospital, La Jolla, California; Taylor D'Amore, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Alberto D. Delgado-Martinez, MD, Hospital Universitario de Jaén, Jaén, Spain; Aydin Gahramanov, MD, Azerbaijan State Medical University, Baku, Azerbaijan: William H. Geerts, MD, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada; Graham S. Goh, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Jesús Gómez-Vallejo, MD, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; Karan Goswami, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Ryan K. Harrison, MD, Indiana University School of Medicine, Indianapolis, Indiana; Andrew J. Hughes, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Dheenadhayalan Jayaramaraju, MD, Ganga Medical Centre & Hospitals Pvt. Limited, Coimbatore, India; Lars G. Johnsen, PhD, Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; Alina Kasimova, MD, Vreden Russian Research Institute of Traumatology and Orthopaedics, Saint Petersburg, Russia; Stephen L. Kates, MD, Virginia Commonwealth University, Richmond, Virginia; James W.M. Kigera, MD, University of Nairobi, Nairobi, Kenya; Justin E. Kleiner, MD, Boston University, Boston, Massachusetts; Chad A. Krueger, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Aleksandar R. Lešić, MD, Clinic of Orthopedic Surgery and Traumatology, Clinical Center of Serbia, Belgrade; Tokifumi Majima, MD, Department of Orthopaedic Surgery, Nippon Medical School, Tokyo, Japan; Kara M. McConaghy, MD, Case Western Reserve University, Cleveland, Ohio; Hasan R. Mohammad, MD, University of Oxford, Oxford, United Kingdom; Jeffrey J. Mojica, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Nestor Moreno-Moreu, MD, Hospital Vithas Santa Catalina, Las Palmas, Gran Canaria, Spain; Banne Nemeth, MD, Leiden University Medical Center, Leiden, Netherlands; Yasushi Oshima, MD, Nippon Medical School, Tokyo, Japan; Francisco Palma-Arjona, MD, Hospital Universitario de Jaén, Jaén, Spain; Hemant G. Pandit, MD, University of Leeds, Leeds, United Kingdom; Javad Parvizi, MD, FRCS, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Nicolas S. Piuzzi, MD, Cleveland Clinic, Cleveland, Ohio; Dragan K. Radoičić, MD, Dr Dren Orthopedic Center, Belgrade, Serbia; Raja Bhaskara Rajasekaran, MD, University of Oxford Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences: Oxford, United Kingdom; Camilo Restrepo, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Tomas Roca-Sanchez, MD, Hospital Vithas Las Palmas, Gran Canaria, Spain; Nigel D. Rossiter, MD, Hampshire Hospitals & The Hampshire Clinic, Basingstoke, United Kingdom; Iván J. Salce, MD, Clínica Delgado, Lima, Peru; Eduardo A. Salvati, MD, Weill Medical College of Cornell University, New York, New York; Charles-Marc Samama, MD, Department of Anaesthesia, Intensive Care and Perioperative Medicine GHU AP-HP Centre, Université de Paris, Cochin Hospital, Paris, France; Velmurugesan P. Sundaram, MD, Ganga Medical Centre & Hospitals Pvt. Limited, Coimbatore, India; Marc F. Swiontkowski, MD, University Of Minnesota department of Orthopaedic Surgery, Minneapolis, Minnesota; Saad Tarabichi, MD, Rothman Orthopaedic Institute, Philadelphia, Pennsylvania; Paul Tornetta III, MD, Boston University Medical Center, Boston, Massachusetts; Nagashree Vasudeva, Ganga Medical Centre & Hospitals Pvt. Limited, Coimbatore, India; MD, Thomas Volk, MD, Department of Anaesthesiology, Intensive Care and Pain Therapy, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany; Geoffrey H. Westrich, MD, Hospital for Special Surgery/Cornell University, New York, New York.