

VTE PROPHYLAXIS EFFECTIVENESS

General Trauma

Byrne, J. P., Geerts, W., Mason, S. A., Gomez, D., Hoeft, C., Murphy, R., . . . Nathens, A. B. (2017). 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*, *82*(2), 252-262. doi:10.1097/TA.000000000000132. This TQIP propensity-matched analysis of 153,474 patients compared LMWH with unfractionated heparin (UF) on preventing PE. LMWH was associated with significantly lower risk of PE. LMWH should be the anticoagulant agent of choice for the prevention of PE in trauma.

Jacobs, B. N., Cain-Nielsen, A. H., Jakubus, J. L., Mikhail, J. N., Fath, J. J., Regenbogen, S. E., & Hemmila, M. R. (2017). Unfractionated heparin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in trauma. *J Trauma Acute Care Surg*, *83*(1), 151-158. doi:10.1097/TA.0000000000001494. This MTQIP study of 18,010 patients compared unfractionated heparin (UFH) vs low molecular weight heparin (LMWH) on trauma patient outcomes. LMWH was superior in reducing the incidence of mortality and VTE events. LMWH should be the preferred VTE prophylaxis agent for use in hospitalized trauma patients.

Pelvic Fractures

Benjamin, E., Aiolfi, A., Recinos, G., Inaba, K., & Demetriades, D. (2019). Timing of venous thromboprophylaxis in isolated severe pelvic fracture: Effect on mortality and outcomes. *Injury*, *50*(3), 697-702 doi:10.1016/j.injury.2019.02.009. This TQIP study of n=2752 blunt AIS>3 pelvic fractures compared early (<48 hr) (73%) vs late (>48 hr) (27%) VTE prophylaxis. 85% received LMWH, and 15% UF. Early VTE prophylaxis is independently associated with improved survival and fewer VTE. LMWH may be preferred over UH for this purpose.

Hamidi, M., Zeeshan, M., Sakran, J. V., Kulvatunyou, N., O'Keeffe, T., Northcutt, A., . . . Joseph, B. (2019). Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin for Thromboprophylaxis in Nonoperative Pelvic Fractures. *Journal of the American College of Surgeons*, *228*(1), 89-97. doi:10.1016/j.jamcollsurg.2018.09.023. This TQIP propensity-matched analysis (n=852) of isolated blunt nonoperative pelvic fracture patients compared LMWH vs DOACs (FXa inhibitor or direct thrombin inhibitor) on DVT/PE outcomes. DOACs were associated with a reduced rate of DVT compared with LMWH, without increasing the risk of bleeding complications.

Jehan, F., O'Keeffe, T., Khan, M., Chi, A., Tang, A., Kulvatunyou, N., . . . Joseph, B. (2017). Early thromboprophylaxis with low-molecular-weight heparin is safe in patients with pelvic fracture managed nonoperatively. *Journal of Surgical Research*, *219*, 360-365. doi:10.1016/j.jss.2017.06.049. This single-center retrospective (2010-2012) study of 255 nonoperative pelvic fracture patients compared (first 24 hr) versus late (after 24 hr) initiation of LMWH prophylaxis. Late LMWH had a higher incidence of symptomatic DVT and longer hospital LOS. Early LMWH in pelvic fractures managed nonoperatively is safe and decreases the risk of symptomatic deep venous thrombosis.

Spinal Trauma

Hamidi, M., Zeeshan, M., Kulvatunyou, N., Mitra, H. S., Hanna, K., Tang, A., . . . Joseph, B. (2019). Operative spinal trauma: Thromboprophylaxis with low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOACs). *J Thromb Haemost*, 17(6), 925-933. doi:10.1111/jth.14439. This 2 year (2015-2016) TQIP propensity-matched analysis of 6036 adult isolated operative spine (AIS>3) injuries compared those receiving either LMWH (94%) or DOACs (6%). This study demonstrates that thromboprophylaxis with DOACs in patients with isolated spinal trauma managed operatively appears to be associated with lower rates of DVT and PE without increasing the rates of bleeding complications or mortality.

Khan, M., Jehan, F., O'Keeffe, T., Hamidi, M., Truitt, M., Zeeshan, M., . . . Joseph, B. (2018). Optimal Timing of Initiation of Thromboprophylaxis after Nonoperative Blunt Spinal Trauma: A Propensity-Matched Analysis. *Journal of the American College of Surgeons*, 226(5), 760-768. This TQIP propensity-matched analysis of 8552 nonoperative, isolated spine trauma patients compared early (<48 hrs) vs late (>48 hrs) thromboprophylaxis. Early thromboprophylaxis was associated with lower DVT and PE. There was no difference in PRBC requirement and mortality.

Zeeshan, M., Khan, M., O'Keeffe, T., Pollack, N., Hamidi, M., Kulvatunyou, N., . . . Joseph, B. (2018). 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*, 85(2), 387-392. This TQIP propensity-matched analysis of 3554 operative adult spine injury patients (spine AIS score >3) compared early (< 48 hrs) to late (>48 hrs) thromboprophylaxis. Early VTE prophylaxis was associated with decreased rates of DVT without increasing the risk of bleeding and mortality. VTE prophylaxis should be started within 48 hrs of surgery to reduce risk of DVT.

Khan, M., Jehan, F., O'Keeffe, T., Hamidi, M., Kulvatunyou, N., Tang, A., . . . Joseph, B. (2018). Oral Xa Inhibitors Versus Low Molecular Weight Heparin for Thromboprophylaxis After Nonoperative Spine Trauma. *Journal of Surgical Research*, 232, 82-87. This 4-yr (2013-2016) TQIP propensity-matched analysis of 1056 isolated nonoperative spine trauma (Spine-AIS >3 and other-AIS <3) compared LMWH versus oral Xa inhibitors (Xa-Inh) thromboprophylaxis. Oral Xa-Inh seems to be more effective than LMWH for VTE prevention in nonoperative spine trauma. The two drugs had similar safety profile. Further prospective trials should be performed to change current guidelines.

Chang, R., Scerbo, M. H., Schmitt, K. M., Adams, S. D., Choi, T. J., Wade, C. E., & Holcomb, J. B. (2017). Early chemoprophylaxis is associated with decreased venous thromboembolism risk without concomitant increase in intraspinal hematoma expansion after traumatic spinal cord injury. *J Trauma Acute Care Surg*, 83(6), 1088-1094. This single-center retrospective study (2012-2015) of 501 patients with spinal cord injury comparing those receiving (<48 hr) heparin vs aspirin chemoprophylaxis on intraspinal hematoma expansion diagnosed intraoperatively or by follow up radiology. Early aspirin was not associated with reduced VTE or PE. Early heparinoid therapy was associated with decreased VTE and PE risk in SCI patients without concomitant increase in ISH expansion.

DiGiorgio, A. M., Tsolinas, R., Alazzeh, M., Haefeli, J., Talbott, J. F., Ferguson, A. R., . . . Dhall, S. S. (2017). Safety and effectiveness of early chemical deep venous thrombosis prophylaxis after spinal cord injury: pilot prospective data. *Neurosurgical Focus*, 43(5), E21. This is a single-center prospective observational study of 49 adult spinal cord injury patients treated at a single Level I trauma center. Standardized VTE prophylaxis was initiated: LMWH (40 mg SQ daily) within 24 hours of injury. Patients undergo surgery within 24 hours of injury and LMWH is withheld for 24 hours after surgery. The standardized protocol was effective in keeping VTE at the lower end of the reported range, and is safe, with a zero rate of adverse bleeding events.

Traumatic Brain Injury

Stormann, P., Osinloye, W., Freiman, T. M., Seifert, V., Marzi, I., & Lustenberger, T. (2019). Early Chemical Thromboprophylaxis Does not Increase the Risk of Intracranial Hematoma Progression in Patients with Isolated Severe Traumatic Brain Injury. *World Journal of Surgery*, 43(11), 2804-2811. doi:10.1007/s00268-019-05072-1. This is a single-center retrospective cohort study of severe blunt TBI with AIS \geq 3. Patients were categorized into 4 groups according to start of VTE chemoprophylaxis: Early (\leq 24 h after hospitalization) n=93, intermediate (24–48 h) n=90, late (\geq 48 h) n=74, and no therapy (no prophylactic anticoagulation within the first five days of hospitalization) n=35. The overall rate of intracranial bleeding progression was 13.6% after prophylactic anticoagulation was started. No statistically significant differences were found in the frequency of intracranial bleeding progression comparing the different time groups (early 12.9% vs. intermediate 11.1% vs. late 17.6%; adj. p = 0.13). The early administration of VTE chemoprophylaxis within 24 h after admission in patients with severe TBI did not increase the risk of intracranial bleeding progression. However, the results of the current study regarding timing of VTE prophylaxis should be interpreted with caution due to the relatively small sample size and low number of VTE events.

Benjamin, E., Recinos, G., Aiolfi, A., Inaba, K., & Demetriades, D. (2017). Pharmacological thromboembolic prophylaxis in traumatic brain injuries: Low molecular weight heparin is superior to unfractionated heparin. *Annals of Surgery*, 266(3), 463-469. This TQIP study of 20,417 severe blunt TBI patients (AIS $>$ 3) compared patients receiving LMWH versus unfractionated heparin (UH) on thrombotic complications. LMWH prophylaxis in severe TBI is associated with better survival and lower thromboembolic complications than UH.

Frisoli, F. A., Shinseki, M., Nwabuobi, L., Zeng, X. L., Adrados, M., Kanter, C., . . . Huang, P. P. (2017). Early Venous Thromboembolism Chemoprophylaxis After Traumatic Intracranial Hemorrhage. *Neurosurgery*, 81(6), 1016-1020. doi:10.1093/neuros/nyx164. This is a single-center propensity-matched cohort analysis of n=282 TBI patients receiving early chemoprophylaxis ($<$ 24 h) 33% were compared to the matched cohort of patients who received heparin in a delayed fashion ($>$ 48 h) 67%. Early ($<$ 24 h) initiation of VTE chemoprophylaxis in patients with traumatic intracranial hemorrhage appears to be safe. Further prospective studies are needed to validate this finding.

Byrne, J. P., Mason, S. A., Gomez, D., Hoeft, C., Subacius, H., Xiong, W., . . . Nathens, A. B. (2016). Timing of pharmacologic venous thromboembolism prophylaxis in severe traumatic brain injury: A propensity-matched cohort study. *Journal of the American College of Surgeons*, 223(4), 621-631.e625. This TQIP propensity-matched analysis 3,634 isolated TBI patients (Head AIS $>$ 3 and GCS score $<$ 8) compared early prophylaxis ($<$ 72 hours) versus late prophylaxis ($>$ 72 hours) using either LMWH or UFH. Early prophylaxis was associated with decreased risk of PE and DVT with no increase in risk of late neurosurgical intervention or death. Early prophylaxis may be safe and should be the goal for each patient in the context of appropriate risk stratification.

VTE PROPHYLAXIS DOSING STRATEGIES

Karcutskie, C. A., Dharmaraja, A., Patel, J., Eidelson, S. A., Padiadpu, A. B., Martin, A. G., . . . Proctor, K. G. (2018). Association of Anti-Factor Xa-Guided Dosing of Enoxaparin with Venous Thromboembolism After Trauma. *JAMA Surg*, 153(2), 144-149. doi:10.1001/jamasurg.2017.3787. This single-center retrospective review of 950 trauma patients assessed anti-factor Xa guided dosing of thromboprophylaxis. The control group received fixed doses of either heparin sodium, 5000 U 3 times a day, or enoxaparin sodium, 30mg twice a day. The adjustment cohort initially received enoxaparin sodium, 30mg twice a day. A peak anti-Xa level was drawn 4 hours after the third dose. If the anti-Xa level was 0.2 IU/mL or higher, no adjustment was made. If the anti-Xa level was less than 0.2 IU/mL, each dose was increased by 10mg. The process was repeated up to a maximum dose of 60 mg twice a day. Rates of VTE were not reduced with anti-Xa-guided dosing, and almost half of the patients never reached prophylactic anti-Xa levels; achieving those levels did not decrease VTE rates. Thus, other targets, such as platelets, may be necessary to optimize thromboprophylaxis after trauma.

Dhillon, N. K., Smith, E. J. T., Gillette, E., Mason, R., Barmparas, G., Gewertz, B. L., & Ley, E. J. (2018). Trauma Updated: 04.01.20

patients with lower extremity and pelvic fractures: Should anti-factor Xa trough level guide prophylactic enoxaparin dose? *Int J Surg*, 51, 128-132. doi:10.1016/j.ijsu.2018.01.023. This single-center prospective study of n=159 lower extremity or pelvic injury who received enoxaparin for VTE prophylaxis. Patients in the control cohort received enoxaparin at 30 mg twice daily. Patients in the adjustment cohort had anti-Xa trough levels measured after three or more consecutive doses of enoxaparin. Those with a trough level of 0.1 IU/mL or lower had their dosage increased by 10-mg increments. Prophylactic enoxaparin adjusted by anti-factor Xa level may lead to a decreased rate of clinically evident VTE among trauma patients with lower extremity and/or pelvic fractures. Our findings indicate that the initial dose of enoxaparin was frequently too low.

Kopelman, T. R., Walters, J. W., Bogert, J. N., Basharat, U., Pieri, P. G., Davis, K. M., . . . Pressman, M. A. (2017). Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. *Injury*, 48(5), 1088-1092. doi:10.1016/j.injury.2016.10.039. This retrospective review of 306 trauma patients having received prophylactic enoxaparin and appropriately timed anti-Xa levels was performed. Dosage was adjusted to maintain an anti-Xa level of 0.3–0.5 IU/ml. Goal anti-Xa levels were met initially in only 46% of patients despite dosing of >40 mg twice daily in 81% of patients; however, with titration, goal anti-Xa levels were achieved in an additional 109 patients (36%). An average enoxaparin dosage of 0.55 mg/kg twice daily was required for adequacy. Bleeding complications were identified in five patients (1.6%) with three requiring intervention. Conclusion: An increased anti-Xa range of 0.3–0.5 IU/ml was attainable but frequently required titration of enoxaparin dosage. This produced a lower rate of DVT than previously published without increased complications.

Singer, G. A., Riggi, G., Karcutskie, C. A., Vaghaiwalla, T. M., Lieberman, H. M., Ginzburg, E., . . . Lineen, E. B. (2016). Anti-Xa-guided enoxaparin thromboprophylaxis reduces rate of deep venous thromboembolism in high-risk trauma patients. *J Trauma Acute Care Surg*, 81(6), 1101-1108. doi:10.1097/TA.0000000000001193. This is a retrospective observational study of patients admitted to a trauma intensive care unit over a 12-month period if they received anti-Xa-guided enoxaparin. Dosage was adjusted to a prophylactic peak anti-Xa level of 0.2 to 0.4 IU/mL. Subgroup analysis was performed on high-risk patients (RAP score ≥10) who received lower-extremity duplex ultrasound surveillance for deep vein thrombosis (DVT). Increased weight, body mass index, ISS, and RAP score are associated with subprophylactic anti-Xa levels. Anti-Xa-guided enoxaparin dosing reduced the rate of DVT from 20.5% to 7.1% in high-risk trauma patients.

Ko, A., Harada, M. Y., Barmparas, G., Chung, K., Mason, R., Yim, D. A., . . . Ley, E. J. (2016). Association between enoxaparin dosage adjusted by anti-factor Xa trough level and clinically evident venous thromboembolism after trauma. *JAMA Surg*, 151(11), 1006-1013. doi:10.1001/jamasurg.2016.1662. This single-institution, historic vs prospective cohort of trauma patients who received enoxaparin adjusted by anti-Xa trough level (adjustment group) were compared with those who received enoxaparin at 30mg twice daily (control group). In this study, sub-prophylactic anti-Xa trough levels were common in trauma patients. Enoxaparin dosage adjustment may lead to a reduced rate of VTE without an increased risk of bleeding.