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CORR Insights

CORR Insights®: Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors?

Daniel R. Whiting MD

Where Are We Now?

In the early era of TKA 40% to 80% of patients developed postoperative venous thromboembolism (VTE) [5, 13]. Although clinicians identified a large portion of these patients during routine postoperative screening studies and found those clots were resolved on followup imaging, great efforts were made to decrease VTE and its associated morbidity and mortality. Patients now mobilize much earlier thanks in large part to improvements in controlling pain and nausea with multimodal analgesia. Early mobilization can generally mitigate the venous stasis portion of Virchow's triad of stasis, hypercoaguability, and intimal injury. Pharmacologic prophylaxis seeks to address the hypercoagulable state of the patient who may not be very mobile in the days immediately after surgery.

Bala and colleagues provide us with the first direct comparison of the four major classes of chemoprophylaxis routinely used in TKA; warfarin, low-molecular-weight heparin (LMWH), aspirin, and factor Xa inhibitors. Although warfarin and LMWH are mainstays in the field, the use of aspirin and factor Xa inhibitors have become more prevalent as concerns regarding warfarin and LMWH, including their need for routine monitoring and the potential for increased bleeding [10, 15], grow louder.

The current study represents a fair assessment of the current state of VTE prophylaxis in TKA; with aspirin and factor Xa inhibitors rising in popularity due to decreased cost, favorable risk profiles, and ease of use, while warfarin and LMWH continue to be used by many clinicians given their proven anticoagulation effects and long history in the field.

Where Do We Need To Go?

The advent of pharmacologic prophylaxis brought about additional risks of postoperative bleeding, hematoma, wound complications, and infection [11]. The need to balance the risks of VTE with those of the prophylactic medications has led to considerable research in the field. However, details regarding the ideal prophylactic regimen remain unsettled and a number of

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D. R. Whiting MD (✉)
Northern Rockies Orthopedics, 2831 Fort Missoula Rd #232, Missoula, MT 59804, USA
e-mail: dwhiting2000@yahoo.com

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questions remain: What is the best prophylactic agent for an individual patient? Which patients have an increased risk for VTE? What is the ideal dose of each agent? And how long should patients receive prophylaxis?

A number of recent studies, including the current study, show that aspirin's low cost, excellent bleeding profile, and seemingly equivalent antithrombotic prophylaxis make it an ideal choice for many patients undergoing TKA [7, 15]. However, aspirin may not provide sufficient anticoagulation for high-risk patients (those with active malignancy, obesity, a history of previous VTE, nicotine use, hormone replacement, and various prothrombotic conditions) [14]. We need additional research on patients at high-risk for VTE in order to find the ideal prophylactic medication for this patient population, as well as to determine whether some risk factors weigh more heavily in a patient's VTE risk profile than others.

Although aspirin is a promising medication, we still need to determine the ideal dose for patients who undergo TKA. Hematology studies [3, 6] demonstrated an antiplatelet effect in most patients with doses greater than 100 mg and no improvement in efficacy with higher doses. Another study [9] indicated that twice daily dosing may provide better inhibition than a single daily dose. Together, these studies provide additional support to a recent report [7] advocating for the usage of 81 mg twice daily after total joint arthroplasty, as it may provide appropriate prophylaxis, while avoiding the increased potential for gastrointestinal side effects that can be seen with higher doses [7]. Still, additional evidence should be established in order to more fully assess its efficacy in this setting.

The current study also shows promising results for factor Xa inhibitors, demonstrating low VTE rates and low complications compared to warfarin and LMWH. But is one factor Xa inhibitor superior to another in the setting of TKA?

Another concern with this relatively new class of medications is the lack of an available reversal agent [12]. This is especially pertinent when considering the potential need to return to the operating room, where surgeons must balance the urgency of the proposed surgery with a medication's associated bleeding risk. A reversal agent may be available in the future, but until that time, surgeons should be aware of the recommendations for the individual medications in this class and discuss it with all those involved.

Determining the ideal duration of treatment is relevant for all of the prophylactic agents. Current clinical practice guidelines recommend a minimum of 10 to 14 days, but suggest extending this to five weeks of treatment after TKA [1, 4]. This wide range of duration should be better defined, especially for those requiring medication that is more expensive or cumbersome to monitor and administer.

Finally, when considering clinical practice guidelines, clinicians should examine the Centers for Medicare & Medicaid Services (CMS) guidelines. Currently, CMS denotes postoperative VTE after TKA as a "never event," denies payment for any treatment of this, and counts it as a sign of lower-quality care [2]. While regulations mandating prophylaxis have certainly encouraged an increased vigilance amongst surgeons, there remains a percentage of VTE that continues to occur even in the setting of recommended prophylactic measures. Many would likely agree that the actions of CMS are justified if a patient develops VTE and appropriate prophylaxis has not been provided. However, when clinical guidelines are followed and a VTE develops, this refusal to provide payment for its treatment and reporting it as a sign of inferior care places an undue burden on local healthcare providers. Organized societies, such as the American Academy of Orthopaedic Surgeons (AAOS) and American Association of Hip and Knee Surgeons (AAHKS), need to continue fighting

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against these unjust policies and for the protection of those practicing medicine in accordance with the best available evidence.

How Do We Get There?

As is the case with many questions in medicine, large, randomized clinical trials provide the highest level of evidence, but are often difficult to perform. Nevertheless, one such trial is currently underway to investigate not only the clinical efficacy of VTE prophylactic regimens, but also patient preferences regarding the balance between VTE prevention and medication complications [8]. The Comparative Effectiveness of Pulmonary Embolism Prevention after Hip and Knee Replacement (PEPPER) trial will include 25,000 patients at 25 centers over two and a half years [8]. Patients will be randomized to receive aspirin 81 mg twice daily, warfarin with a goal international normalized ratio of 1.7 to 2.2, or rivaroxaban 10 mg. Prophylactic medications will be given for 30 days postoperatively, and all patients will receive pneumatic compression devices while in the hospital.

This exciting and well-structured study is sure to provide insight into both the efficacy and risks of these medications, but additional questions will remain and new questions will arise in the future. We will not be able to perform such a large randomized study to answer all of these future questions, but one tool that could help facilitate their study is the establishment of a standardized risk assessment profile to identify patients as being either high or low-risk for VTE.

The development of such a tool is a prime opportunity for the AAOS or AAHKS to facilitate advancement in the field and ultimately improve patient care. Adherence to a standardized stratification protocol would allow for a more accurate comparison across different treatment groups. We could then facilitate the combination of patient groups from across the country in order to attain sufficient power to demonstrate potential differences in these rare events. This would not only improve the quality of individual studies, but would also improve our ability to conduct potential comparison studies and provide the highest level of care for each of our patients.

References

1. American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Available at: https://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf. Accessed June 23, 2017.
2. Centers for Medicare & Medicaid Services. Final rule-Inpatient prospective payment system with hospital value-based purchasing program provisions for FY 13, 14, 16. Available at: http://www.gpo.gov/fdsys/pkg/FR-2012-08-31/pdf/2012-19079.pdf. Accessed June 23, 2017.
3. Ellis EF, Wright KF, Jones PS, Richardson DW, Ellis CK. Effect of oral aspirin dose on platelet aggregation and vascular prostacyclin (PGI2) synthesis in humans and rabbits. *J Cardiovas Pharmacol*. 1980;2:387–397.
4. 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;141(2 suppl): e278S–e325S.
5. Francis CW, Pellegrini VD Jr, Stulberg BN, Miller ML, Totterman S, Marder VJ. Prevention of venous thrombosis after total knee arthroplasty. Comparison of antithrombin III and low-dose heparin with

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dextran. *J Bone Joint Surg Am*. 1990; 72:976–982.
6. Malhotra S, Sharma YP, Grover A, Majumdar S, Hanif SM, Bhargava VK, Bhatnagar A, Pandhi P. Effect of different aspirin doses on platelet aggregation in patients with stable coronary artery disease. *Intern Med J*. 2003;33:350–354.
7. Parvizi J, Huang R, Restrepo C, Chen AF, Austin MS, Hozack WJ, Lonner JH. Low-dose aspirin is effective chemoprophylaxis against clinically important venous thromboembolism following total joint arthroplasty: A preliminary analysis. *J Bone Joint Surg Am*. 2017;99:91–98.
8. Patient-Centered Outcomes Research Institute. Comparative effectiveness of pulmonary embolism prevention after hip and knee replacement (PEPPER): Balancing safety and effectiveness. Available at: http://www.pcori.org/research-results/2015/comparative-effectiveness-pulmonary-embolism-prevention-after-hip-and-knee. Accessed June 22, 2017.
9. Perneby C, Wallén NH, Rooney C, Fitzgerald D, Hjemdahl P. Dose and time-dependent antiplatelet effects of aspirin. *Thromb Haemost*. 2006;95: 652–658.
10. Sachs RA, Smith JH, Kuney M, Paxton L. Does anticoagulation do more harm than good? A comparison of patients treated without prophylaxis and patients treated with low-dose warfarin after total knee arthroplasty. *J Arthroplasty*. 2003;18: 389–395.
11. Schulman S, Beyth RJ, Kearon C, Levin MN. American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(6 Suppl):257S–298S.
12. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373: 2413–2424.
13. Stringer MD, Steadman CA, Hedges AR, Thomas EM, Morley TR, Kakkar VV. Deep vein thrombosis after elective knee surgery: An incidence study in 312 patients. *J Bone Joint Surg Br*. 1989;71:492–497.
14. White RH, Henderson MC. Risk factors for venous thromboembolism after total hip and knee replacement surgery. *Curr Opin Pulmonary Med*. 2002;8:365–371.
15. Wilson DG, Poolel WE, Chauhan SK, Rogers BA. Systematic review of aspirin for thromboprophylaxis in modern elective total hip and knee arthroplasty. *Bone Joint J*. 2016;98B: 1056–1061.