

Pulmonary Embolism While on Aspirin for Venous Thromboembolism Prophylaxis After Total Knee Arthroplasty

Journal of Primary Care & Community Health
Volume 9: 1–5
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2150132718797446
journals.sagepub.com/home/jpc



Francisco Roman¹, Jay-Sheree Allen¹, Heather Catherine Wurm¹,
and Kathy MacLaughlin¹

Abstract

A 62-year-old Caucasian man with past medical history significant for coronary artery disease, status post drug eluting stent to the left anterior descending artery 10 years prior, was admitted for elective total right knee arthroplasty. His intraoperative course was uneventful, and he was discharged on hospital day 2 on aspirin 325 mg twice daily for 6 weeks for venous thromboembolism (VTE) prophylaxis. Three weeks later the patient developed chest pain shortly after an approximately 1-hour flight and presented to a local emergency department where computed tomography angiogram showed pulmonary emboli involving segmental and subsegmental pulmonary arteries bilaterally. He was transitioned from aspirin 325 mg twice a day to rivaroxaban 15 mg twice daily for 21 days, with a plan to transition to 20 mg daily to complete a 3-month course. He returned to his primary care physician 6 days after discharge with questions about his current anticoagulation therapy as well as the regimen he was on prior to the pulmonary embolism. Two major organizations, The American Academy of Orthopedic Surgeons and The American College of Chest Physicians, provide recommendations for VTE prophylaxis, but they differ regarding the preferred pharmacologic modality and duration. Although the goal is to provide optimal patient care, lack of guideline consensus may lead to different postoperative recommendations. It is important for clinicians to discuss with their patients the pharmacologic options available for VTE prophylaxis, how organizations differ in their recommendations, and the limitations of these pharmacologic agents.

Keywords

total knee arthroplasty, pulmonary embolism, anticoagulation, aspirin, venous thromboembolism prophylaxis

Case Presentation

A 62-year-old Caucasian man with a past medical history significant for coronary artery disease, status post drug eluting stent to the left anterior descending artery (LAD) 10 years prior, was admitted for elective total right knee arthroplasty. The patient underwent combined general and regional anesthesia with a total operative time of 70 minutes. The patient's intraoperative course was uneventful with no immediate complications. Postoperatively the patient made use of sequential compression devices and participated in physical therapy the day after surgery.

He was discharged on hospital day 2 with aspirin 325 mg twice daily for duration of 6 weeks for venous thromboembolism (VTE) prophylaxis. Three weeks later the patient developed chest tightness and pain while on vacation 300 miles away from his home, having traveled by airplane. He presented to a local medical facility where computed tomography angiogram showed numerous pulmonary emboli involving segmental and

subsegmental pulmonary arteries bilaterally along with a small element extending into the right main pulmonary artery. Ultrasound of the right leg did not show a deep vein thrombosis (DVT) and an ultrasound of the leg left was not done.

He was started on rivaroxaban 15 mg twice daily for 21 days with a plan to transition to 20 mg daily to complete a 3-month course and advised to follow up with his primary physician in 1 week. At the subsequent appointment with his primary care physician he was curious about the course of events and had questions regarding his current anticoagulation therapy as well as the regimen that he was on prior to the pulmonary embolism (PE).

¹Mayo Clinic, Kasson, MN, USA

Corresponding Author:

Jay-Sheree Allen, Mayo Family Clinic Kasson, 411 West Main Street,
Kasson, MN 55944, USA.
Email: allen.jays@gmail.com



Table 1. Guidelines for Prevention of VTE by The American Academy of Orthopedic Surgeons (AAOS)⁴ and The American College of Chest Physicians (ACCP)⁵.

AAOS	ACCP
<ul style="list-style-type: none"> • We suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty, and who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding. (<i>Grade of recommendation: Moderate</i>) • Current evidence is unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. Therefore, we are unable to recommend for or against specific prophylactics in these patients. (<i>Grade of recommendation: Inconclusive</i>) • In the absence of reliable evidence about how long to employ these prophylactic strategies, it is the opinion of this work group that patients and physicians discuss the duration of prophylaxis. (<i>Grade of recommendation: Consensus</i>) 	<ul style="list-style-type: none"> • In patients undergoing major orthopedic surgery, we recommend the use of one of the following rather than no antithrombotic prophylaxis: low-molecular-weight heparin; fondaparinux; dabigatran, apixaban, rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery); low-dose unfractionated heparin; adjusted-dose vitamin K antagonist; aspirin (<i>all grade 1B</i>) or an intermittent pneumatic compression device (IPCD) (<i>grade 1C</i>) for a minimum of 10 to 14 days. • We suggest the use of low-molecular-weight heparin in preference to the other agents we have recommended as alternatives (<i>grade 2C/2B</i>). • In patients receiving pharmacologic prophylaxis, we suggest adding an IPCD during the hospital stay (<i>grade 2C</i>). • We suggest extending thromboprophylaxis for up to 35 days (<i>grade 2B</i>). • In patients at increased bleeding risk, we suggest an IPCD or no prophylaxis (<i>grade 2C</i>). • In patients who decline injections, we recommend using apixaban or dabigatran (<i>all grade 1B</i>).

Background

Total joint arthroplasties are common elective procedures performed for pain relief and return of joint function. Primary care providers are often requested to perform the preanesthetic medical evaluations to clear patients for surgery. During these medical evaluations, providers are responsible not only for evaluating a patient's intraoperative cardiac risk but also must address risk for complications in the postoperative period. Orthopedic surgeons assume responsibility for the procedure and for intra and postoperative complications, including VTE prevention.

It is estimated that approximately 900 000 Americans, both male and female, of all ages are affected by VTE events each year.¹ VTE is associated with a cost of approximately \$7 billion to \$10 billion annually.² Approximately 50% of episodes are associated with recent hospitalization or recent surgery.¹ Annually, there are more than 1 million total knee arthroplasty (TKA) and total hip arthroplasty (THA) procedures performed in the United States. A recent observational study suggests that rates of VTE in primary TKA may be as high as 3.5 with prophylaxis.³ Pharmacologic thromboprophylaxis is reported to reduce the risk of VTE after TKA although there is debate in the medical literature over the ideal pharmacologic agent to be used.

The American Academy of Orthopedic Surgeons (AAOS) and The American College of Chest Physicians (ACCP) are national organizations that provide recommendations for post TKA VTE prophylaxis (Table 1). AAOS and ACCP both advise that pharmacologic VTE prophylaxis be combined

with mechanical compressive devices while in the hospital for optimal results.^{4,5} Although both organizations endorse the same pharmacologic agents for VTE prophylaxis—low-molecular-weight heparin (LMWH), aspirin, unfractionated heparin (UFH), warfarin, fondaparinux (Arixta), apixaban (Eliquis), rivaroxaban (Xarelto), and dabigatran (Pradaxa)—2 notable differences include recommendations regarding the preferred pharmacologic modality and duration of VTE prophylaxis. AAOS guidelines recommend no one pharmacologic agent over another with duration of prophylaxis post TKA being patient-provider dependent.⁴ In contrast, ACCP recommends LMWH as the preferred pharmacologic agent for 10 to 14 days, but ideally 35 days.^{4,5}

Review of Literature

In the case presented, appropriate guideline-based recommendations were made using aspirin for VTE prophylaxis after TKA. However, the patient's resultant pulmonary embolism and questions about his management illustrate the importance of understanding all pharmacologic options for prophylaxis. Differences in study designs and conflicting results have created debate in the field and led to different VTE prevention strategies being used post TKA.

The Pulmonary Embolism Prevention (PEP) trial was a prospective randomized trial that evaluated 160 mg of aspirin daily for 35 days versus placebo. The trial demonstrated that among patients with a hip fracture, aspirin produced proportional reductions in PE of 43% and 29% in symptomatic DVT. A smaller group of elective hip arthroplasty patients were

Table 2. Pharmacologic Agents Used for Venous Thromboembolism Prophylaxis, Usual Doses, and Mechanism of Action.^a

Drug	Dosing	Mechanism of Action
Aspirin	Variable dosing strategies	Inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A ₂ , via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation.
Low-molecular-weight heparin	30 mg every 12 hours or 40 mg once daily	Strongly inhibit factor Xa and have a small effect on the activated partial thromboplastin time.
Apixaban (Eliquis)	2.5 mg twice daily	Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound factor Xa (FXa). FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin.
Rivaroxaban (Xarelto)	10 mg daily	Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound factor Xa (FXa). FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin.
Fondaparinux (Arixtra)	2.5 mg once daily	A synthetic pentasaccharide that causes an antithrombin III-mediated selective inhibition of factor Xa. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits thrombin formation and thrombus development.
Dabigatran (Pradaxa)	220 mg once daily	Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI, and XIII, and inhibition of thrombin-induced platelet aggregation.
Warfarin	Dosing is individualized to goal international normalized ratio 2-3	Competitively inhibits the subunit I of the multiunit vitamin K epoxide reductase VKOR complex, thus depleting functional vitamin K reserves and hence reduces synthesis of active clotting factors.

^a Lexicomp.²⁰

included in the PEP study and there was a 34% reduction in risk of VTE (DVT or PE).⁶ The study has several limitations, including allowing additional VTE prophylaxis as deemed necessary by providers, with a high number of patients being on LMWH or UFH. Results from several studies focused on VTE prevention in joint arthroplasty suggested aspirin may be inferior to LMWH, had mixed results compared to warfarin, and led to an increased risk of bleed.⁷⁻⁹

One observational study found LMWH reduced 3-month mortality compared with aspirin. Two other observational studies found aspirin to reduce risk of symptomatic DVT/PE compared with warfarin.⁹⁻¹¹ While another observational study found no difference in outcomes among different pharmacologic agents, including aspirin.^{2,12}

Appropriate assessment of literature regarding aspirin use as first line is difficult given fluctuations in design among studies, such as evaluating either or both symptomatic and asymptomatic DVT/PE, knee and/or hip arthroplasties, dosing strategies, allowance of additional VTE prophylaxis modalities at discretion of provider, and overlap coverage with an additional pharmacologic agent not being assessed.

Factor Xa inhibitors were recently included as another option for postoperative VTE prevention. The mechanism of action of these drugs and other pharmacologic agents used for DVT prophylaxis are outlined in Table 2. The results from the RECORD trials demonstrated that rivaroxaban may be superior to enoxaparin regardless of dosing strategy used for enoxaparin in reducing adverse outcomes, including DVT, nonfatal PE, and mortality, but with a slight increased risk of major bleeding events. In the ADVANCE trials, apixaban also demonstrated superiority over enoxaparin but with a reduced risk of bleeding events. It is worthwhile to note that the superiority of apixaban in reducing these outcomes was only seen when compared with enoxaparin dosed as 40 mg once daily but not as 30 mg twice a day.¹³⁻¹⁹

A large database analysis assessed VTE incidence post TKA with aspirin, warfarin, enoxaparin, and factor Xa inhibitors used as chemoprophylaxis. The results suggested incidence of VTE was lowest with Xa inhibitors, but with a higher incidence of bleeding complications, with results varying at different time points of evaluation (2 weeks, 30 days, 42 days, and 90 days).²¹ The comparable results but

Table 3. Potential Advantages and Disadvantages to Different Pharmacologic Agents Used for Venous Thromboembolism Prophylaxis.

Drug	Advantage	Disadvantage
Aspirin	Low-cost, no prescription needed, oral route of administration	Variable dosing strategies, optimal dose unknown, gastrointestinal intolerance
Low-molecular-weight heparin	May be dosed once daily, approved in pregnancy	Route is injectable, pork-based ingredient, renally eliminated
Apixaban (Eliquis)	Oral route of administration, administer without regard to meals, may be crushed	Twice a day dosing, renally eliminated, cost
Rivaroxaban (Xarelto)	Oral route of administration, once daily dosing, may be crushed	Cost, administration with food recommended if dose greater than 10 mg, renally cleared, pregnancy risk
Fondaparinux (Arixtra)	Once a day dosing	Injectable route of administration, cost, renally cleared
Dabigatran (Pradaxa)	May administer without regard to meals, oral administration	Risk with pregnancy, renally cleared, non-Food and Drug Administration approved indication
Warfarin	Monitoring available, cost, oral administration, disregard renal function, once daily dosing, reversal agent available	Need for monitoring, individualized dosing strategies, drug-drug interactions, drug-food interactions, risk of prothrombotic state at initiation, risk with pregnancy

trend toward more of a positive outcome in these studies suggest new oral anticoagulants may be more favorable. However, the long-term studies with LMWH currently may still make it a more desirable choice.¹³

Given all the available pharmacologic options, indirect comparisons of all, and varied results, it is understandable how challenging managing patients post TKA may be. Additional factors to be reviewed that modify risk for thrombosis include the type of anesthesia used. Multiple studies have shown that neuraxial anesthesia alone or in combination with general anesthesia reduces the rate of thromboembolic complications, including DVT and PE.^{22,23}

Teaching Point

Clinicians often rely on national guidelines for medical management decision making but assessing the risk and benefit of postoperative VTE prevention options is especially challenging given the lack of consensus on best approach. The patient's medical history, including prior episodes of VTE or bleeding diathesis, intraoperative complications, postoperative risks, and plans for long trips in the near future and other provoking factors should play a role in the decision-making process. Additionally, affordability, frequency of dosing, drug-drug interactions, needle aversion, and monitoring requirements should be considered along with potential advantages and disadvantages outlined in Table 3. Discussion with the patient using a shared decision-making approach is also important to ensure that patient priorities are understood and incorporated into the VTE prevention plan.^{24,25}

Acknowledgments

The authors are grateful for the assistance on this case report by the following individuals: Dr Mark Ciota, Orthopedic Surgeon in the Mayo Clinic Health System and Dr Kurt Angstman, Family Medicine Physician at the Mayo Clinic in Rochester.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

- Centers for Disease Control and Prevention. Healthcare-associated venous thromboembolism. <https://www.cdc.gov/ncbddd/dvt/ha-vte.html>. Accessed May 31, 2018.
- Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res*. 2016;137:3-10.
- Cafri G, Paxton EW, Chen Y, et al. Comparative effectiveness and safety of drug prophylaxis for prevention of venous thromboembolism following total knee replacement. *J Arthroplasty*. 2017;32:3524-3528.e1.
- Jacobs JJ, Mont MA, Bozic KJ, et al. 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;94:746-747.

5. Falck-Ytter Y, Francis CW, Johanson NA, et al. 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. doi:10.1378/chest.11-2404.
6. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. *Lancet*. 2000;355:1295-1302.
7. Brookenthal KR, Freedman KB, Lotke PA, Fitzgerald RH, Lonner JH. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. *J Arthroplasty*. 2001;16:293-300.
8. Westrich GH, Haas SB, Mosca P, Peterson M. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. *J Bone Joint Surg Br*. 2000;82:795-800.
9. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: a non-randomised comparison from information in the National Joint Registry. *J Bone Joint Surg Br*. 2011;93:1465-1470.
10. Bozic KJ, Vail TP, Pekow PS, Maselli JH, Lindenauer PK, Auerbach AD. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? *J Arthroplasty*. 2010;25:1053-1060.
11. Raphael IJ, Tischler EH, Huang R, Rothman RH, Hozack WJ, Parvizi J. Aspirin: an alternative for pulmonary embolism prophylaxis after arthroplasty? *Clin Orthop Relat Res*. 2014;472:482-488.
12. Gesell MW, Valle AGD, García SB, et al. Safety and efficacy of multimodal thromboprophylaxis following total knee arthroplasty: a comparative study of preferential aspirin vs routine coumadin chemoprophylaxis. *J Arthroplasty*. 2013;28:575-579.
13. Ericsson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358:2765-2775.
14. Kakkar AK, Brennan B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double blind, randomized controlled trial. *Lancet*. 2008;372:31-39.
15. Lassen MR, Ageno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358:2776-2786.
16. Turpie AG, Lassen MR, Davidson BL, et al; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009;373:1673-1680.
17. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med*. 2009;361:594-604.
18. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375:807-815.
19. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363:2487-2498.
20. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc; 2000. <http://online.lexi.com>. Accessed June 9, 2018.
21. 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;475:2205-2213.
22. Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. *J Bone Joint Surg Br*. 2009;91:935-942.
23. Butterworth JF 4th, Mackey DC, Wasnick JD, eds. *Morgan & Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.
24. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med*. 1997;44:681-692.
25. Mayo Clinic Shared Decision Making National Resource Center. Home page. <https://shareddecisions.mayoclinic.org/>. Accessed June 1, 2018.

Author Biographies

Francisco Roman did his pharmacy training at The University of Texas at Austin/El Paso and residency training at Hennepin County Medical Center. He is currently a clinical pharmacist at Mayo Clinic and his main focus is in Family Medicine.

Jay-Sheree Allen is a Board-Certified Family Medicine Physician. She recently completed her training at the Mayo Clinic and will begin her National Health Service Corps Primary Care commitment in a small rural hospital in Central Minnesota.

Heather Catherine Wurm did her medical training at the University of Minnesota and residency intern training at Hennepin County Medical Center and subsequently Cardiac Anesthesiology training at Mayo Clinic. She is a Cardiac Anesthesiologist with Associated Anesthesiologist PA group working in the Twin Cities.

Kathy MacLaughlin is an assistant professor of Family Medicine at Mayo Clinic Rochester engaged in clinical practice and research. Her research interests include women's health topics, particularly cervical cancer screening guideline compliance through use of clinical decision support systems and improvement in HPV vaccination uptake.