


Use of Fondaparinux Following Elective Lumbar Spine Surgery Is Associated With a Reduction in Symptomatic Venous Thromboembolism

Mitchell S. Fourman, MD, MPhil¹ , Jeremy D. Shaw, MD, MS¹, Chinedu O. Nwasike, MD¹, Lorraine A. T. Boakye, MD¹, Malcolm E. Dombrowski, MD¹, Nicholas J. Vaudreuil, MD¹, Richard A. Wawrose, MD¹, David J. Lunardini, MD², and Joon Y. Lee, MD¹

Global Spine Journal
2020, Vol. 10(7) 844-850
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2192568219878418
journals.sagepub.com/home/gsj



Abstract

Study Design: Retrospective cohort study.

Objective: To assess the impact of fondaparinux on venous thromboembolism (VTE) following elective lumbar spine surgery in high-risk patients.

Methods: Matched patient cohorts who did or did not receive inpatient fondaparinux starting postoperative day 2 following elective lumbar spine surgery were compared. All patients received 1 month of acetyl salicylic acid 325 mg following discharge. The primary outcome was a symptomatic DVT (deep vein thrombosis) or PE (pulmonary embolus) within 30 days of surgery. Secondary outcomes included prolonged wound drainage, epidural hematoma, and transfusion.

Results: A significantly higher number of DVTs were diagnosed in the group that did not receive inpatient VTE prophylaxis (3/102, 2.9%) compared with the fondaparinux group (0/275, 0%, $P = .02$). Increased wound drainage was seen in 18.5% of patients administered fondaparinux, compared with 25.5% of untreated patients ($P = .15$). Deep infections were equivalent (2.2% with fondaparinux vs 4.9% control, $P = .18$). No epidural hematomas were noted, and the number of transfusions after postoperative day 2 and 90-day return to operating room rates were equivalent.

Conclusions: Patients receiving fondaparinux had lower rates of symptomatic DVT and PE and a favorable complication profile when compared with matched controls. The retrospective nature of this work limits the safety and efficacy claims that can be made about the use of fondaparinux to prevent VTE in elective lumbar spine surgery patients. Importantly, this work highlights the potential safety of this regimen, permitting future high-quality trials.

Keywords

venous thromboembolism prophylaxis, adult spine, fondaparinux, high-risk, deep vein thrombosis, pulmonary embolism

Introduction

The prevention of venous thromboembolism (VTE) following orthopedic procedures has largely focused on the trauma and adult reconstruction populations.¹⁻⁶ However, the incidence of pulmonary embolus (PE) and deep venous thrombosis (DVT) following spine surgery has been reported to be as high as 18% and 19%, respectively^{7,8} Hohl et al⁹ in their multi-institutional study of patients who underwent elective thoracolumbar

¹ University of Pittsburgh Medical Center, Pittsburgh, PA, USA

² University of Vermont Medical Center, Burlington, VT, USA

Corresponding Author:

Joon Y. Lee, University of Pittsburgh Medical Center, Suite 1010, Kaufmann Medical Building, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA.
Email: leejy3@upmc.edu



surgery reported an overall VTE prevalence of 1.5%, of symptomatic PE 0.88%, and of DVT 0.66%. They also reported that while patients >65 years old at the time of surgery had a 2.196 times higher prevalence of DVT and PE, sex, instrumentation, and revision surgery were not risk factors for VTE. A National Surgical Quality Improvement Program (NSQIP) study by Schoenfeld et al¹⁰ found a 1% incidence of VTE after spine surgery at any level, with a significantly increased risk of DVT seen in patients with a body mass index ≥ 40 kg/m², age ≥ 80 years, operative time >261 minutes, and American Society of Anesthesiologists classification of ≥ 3 .

There is currently no gold standard for the administration of VTE prophylaxis following elective spine surgery. Current recommendations are based on limited evidence, and proposed algorithms remain controversial. Recent work suggests that the risk of bleeding complications after elective spine surgery is negligible when weight-based subcutaneous heparin or low-molecular-weight heparin is started 24 hours after surgery.^{11,12} Fondaparinux, a once-a-day injectable, has been found to have an equivalent benefit, risk reduction, and complication rate after total joint surgery compared with multidose enoxaparin.¹³ However, its utility as chemoprophylaxis after spine surgery has not been established.

The purpose of the present study was to assess the impact of fondaparinux on VTE following elective lumbar spine surgery in high-risk patients. We hypothesized that fewer VTEs would occur in patients administered fondaparinux compared with matched peers, without an increased risk of postoperative complications.

Methods

Study Population and Patient Selection

In a University of Pittsburgh Institutional Review Board-approved protocol (#PRO14090068), a retrospective analysis of 6 years (January 2009 to December 2015) of patients who underwent elective lumbar (including thoracolumbar junction and lumbosacral) spine procedures was performed. Patients who received any other VTE prophylaxis during their inpatient stay (ie, warfarin, heparin, etc) were excluded from this analysis. Both primary and revision procedures were included. All patients had 7-French drains placed intraoperatively, with the number of drains dependent on intraoperative bleeding.

Venous Thromboembolic Prophylaxis

All patients received mechanoprophylaxis with pneumatic compression devices postoperatively and were prescribed 30 days of acetyl salicylic acid (ASA) 325 mg following discharge. Patients who were at a higher medical risk of developing a postoperative VTE were identified according to criteria listed in Figure 1. In those patients, fondaparinux 2.5 mg subcutaneous daily was started on postoperative day 2 and continued throughout admission. The selection of fondaparinux was due to its once-a-day dosing and equivalent safety profile in

Absolute Selection Criteria:

1. Revision Procedure
2. Multi-Level Fusion
3. History of Prior DVT/PE
4. Anterior/Posterior Procedure
5. Current Hormone Replacement Therapy
6. Meets Relative Selection Criteria and Cannot Ambulate on POD#1

Relative Selection Criteria:

1. COPD
2. Current Tobacco Use
3. Diabetes
4. Elevated BMI (≥ 30)
5. History of Cancer

Figure 1. Absolute and relative selection criteria for the use of fondaparinux starting on postoperative day 2.

arthroplasty patients.^{14,15} Drains were maintained for at least 24 hours after the start of fondaparinux, then removed based on output.

Data Collection

In addition to the high-risk criteria used to indicate fondaparinux prophylaxis, patient characteristics used to establish a matched cohort included age on the date of surgery, gender, and Age-Adjusted Charlson Comorbidity Index (AACCI).¹⁶

The primary outcome measure was the incidence of a symptomatic DVT within 30 days of surgical intervention. Secondary outcomes included pulmonary embolism, epidural hematoma, minor wound complications that resolved without operative intervention, and major wound complications that required a return to the operating room. All recorded thromboembolic diagnoses were confirmed using venous duplex ultrasound for DVT and chest computed tomography (CTPE) for PE.

Statistical Analysis

Data are reported as mean \pm standard deviation for continuous variables, and as percentages for categorical variables. Continuous variables were compared using the Student's *t* test, while dichotomous variables were compared using Fisher's exact test. Statistical analyses were performed by the investigators using GraphPad Prism 7.0 (La Jolla, CA), with significance defined as $P < .05$.

Results

A total of 724 patients underwent elective spine surgery during the study period. Of these, 377 met high-risk patient criteria (Figure 2); 275 received fondaparinux followed by 30 days of ASA following discharge, while 102 received outpatient ASA

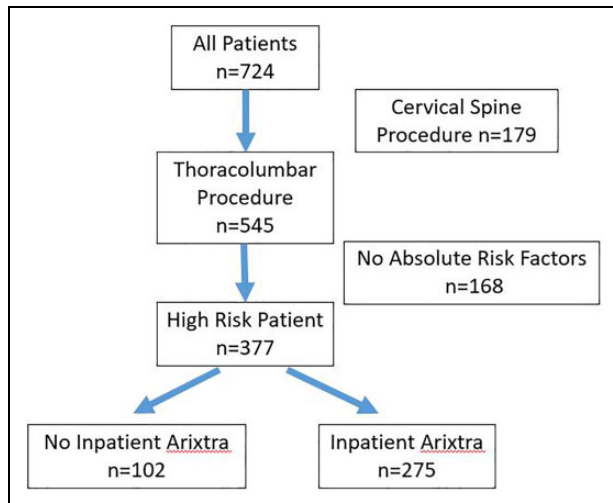


Figure 2. Patient selection flowchart.

Table 1. Patient Inclusion by Absolute Risk Factor.

	ASA Only (N = 102), n (%)	Arixtra + ASA (N = 275), n (%)	P
Revision procedure	54 (52.9)	135 (49.1)	.56
Multilevel (>1) fusion	63 (61.8)	227 (82.5)	<.0001 ^a
History of prior DVT/PE	13 (12.7)	22 (8.0)	.17
Anterior/posterior procedure	3 (2.9)	4 (1.5)	.39
Current hormone replacement therapy	2 (2.0)	13 (4.7)	.37
Relative risk factors + unable to ambulate POD1	4 (3.9)	21 (7.6)	.25
Absolute risk factors, mean ± SD	1.5 ± 0.6	2.3 ± 1.0	.01 ^a

Abbreviations: ASA, acetyl salicylic acid; DVT, deep venous thrombosis; PE, pulmonary embolism; POS1, postoperative day 1.

^aStatistically significant ($P < .05$).

alone. Matched cohorts based on absolute risk factors were established (Table 1). An equivalent proportion of patients met each criterion in the ASA-only and the fondaparinux + ASA groups, except for those who underwent multilevel fusions (63/102, 61.8% in ASA-only group vs 227/275, 82.5% in the fondaparinux + ASA group, $P < .0001$). The mean number of absolute risk factors was also significantly greater in the fondaparinux + ASA group (2.3 ± 1.0 vs 1.5 ± 0.6 in the ASA-only group, $P = .01$). Patient characteristics in each cohort are shown in Table 2.

Three patients in the ASA-only group and no patients in the fondaparinux + ASA group were diagnosed with a DVT (3/102, 2.9%) within 30 days of hospital admission ($P = .02$, Table 3). Two ASA-only patients (2/102, 2.0%) and 1 fondaparinux + ASA patient developed PEs (1/275, 0.4%, $P = .49$). The incidence of deep infections (6/275, 2.2% with fondaparinux + ASA vs 5/102, 4.9% with ASA-only, $P = .18$) and gross wound dehiscence were also equivalent (4/275, 1.5% with fondaparinux + ASA vs 2/102, 2% with ASA-only, $P = .66$). No epidural

Table 2. Study Patient Characteristics.

	ASA Only (N = 102)	Arixtra + ASA (N = 275)	P
Age at time of surgery, y, mean ± SD	59.0 ± 14.5	61.7 ± 13.0	.08
Male gender, n (%)	46 (45.1)	111 (40.4)	.41
BMI, kg/m ² , mean ± SD	30.8 ± 7.7	31.3 ± 6.7	.59
Age-Adjusted Charlson Comorbidity Index, mean ± SD	2.7 ± 2.0	2.9 ± 1.9	.59
Length of surgery, min, mean ± SD	166.6 ± 105.7	191.1 ± 77.4	.01 ^a
Hospital length of stay, d, mean ± SD	4.4 ± 2.5	4.5 ± 1.7	.47
Current tobacco use, n (%)	36 (35.3)	72 (26.2)	.10
COPD, n (%)	6 (5.9)	14 (5.1)	.80
Diabetes, n (%)	25 (24.5)	69 (25.1)	>.99
Obesity (BMI ≥ 30 kg/m ²), n (%)	50 (49)	156 (56.7)	.20
Morbid Obesity (BMI ≥ 40 kg/m ²), n (%)	10 (9.8)	27 (9.8)	>.99
History of cancer, n (%)	14 (13.7)	26 (9.4)	.26

Abbreviations: ASA, acetyl salicylic acid; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

^aStatistically significant ($P < .05$).

Table 3. Clinical Complications.

	ASA Only (N = 102), n (%)	Fondaparinux + ASA (N = 275), n (%)	P
Prolonged wound drainage/high drain output	26 (25.5)	51 (18.5)	.15
Deep infection	5 (4.9)	6 (2.2)	.18
Wound dehiscence	2 (2.0)	4 (1.5)	.66
90-day return to OR	8 (7.8)	11 (4.0)	.18
DVT	3 (2.9)	0 (0)	.02 ^a
PE	2 (2.0)	1 (0.4)	.49
Epidural hematoma	0 (0)	0 (0)	1.0
Transfusion after POD2	8 (8.2)	38 (15.0)	.16

Abbreviations: ASA, acetyl salicylic acid; OR, operating room; DVT, deep venous thrombosis; PR, pulmonary embolism; POD2, postoperative day 2.

^aStatistically significant ($P < .05$).

hematomas were diagnosed in either group and an equivalent number of packed red blood cell transfusions after postoperative day 2 were required (8/102, 8.2% in ASA-only vs 38/275, 15.0% in fondaparinux + ASA, $P = .16$). Eight patients in the ASA-only group required a return to operating room for infectious or drainage complication (7.8%), while 11 in the fondaparinux + ASA group required the same (11/275, $P = .18$).

Discussion

In a retrospective analysis of a 6-year experience using inpatient fondaparinux in addition to home ASA as VTE

chemoprophylaxis in select high-risk patients, patients administered fondaparinux had a significantly lower incidence of symptomatic DVTs, without an increased risk of postoperative complication. While prospective validation is required, the present study suggests that fondaparinux should be considered in patients with medical comorbidities that place them at a higher risk of perioperative VTE.

Current literature on VTE prophylaxis after elective spine surgery is underpowered,¹⁷ heterogeneous,¹⁸ or utilizes nonvalidated surgeon-response metrics.¹⁹ Survey studies by Ploumis et al²⁰ and Glotzbecker et al²¹ criticize the inconsistent application of VTE prophylaxis after high-risk spine procedures, noting that even spinal cord injuries did not clearly delineate common practice. This echoes prior reservations expressed in existing literature over the past 3 decades,²² and may be related to vagaries in current recommendations. However, multifactorial medical comorbidity imparts a clear risk of VTE following elective spine surgery.

Retrospective works and national database studies on VTE after elective spine surgery suffer from underdiagnosis and systematic reporting bias. These studies report an incidence of DVT and PE following elective spine procedures of 0.78% to 2.5% and 0.06% to 0.8%, respectively.^{17,23-26} Prospective, universal screening protocols report an exponentially higher incidence of VTE. Takahashi et al⁷ performed contrast-enhanced CT on 100 patients 1 week after elective spine surgery, identifying asymptomatic PEs in 18% of patients. This is similar to the CT screening protocol performed by Inoue et al,⁸ who identified asymptomatic VTEs in 13% (PE in 8%) of patients. Tominaga et al²⁷ performed lower extremity duplex ultrasound on 80 patients following elective spine surgery, identifying DVTs in 25%. This incidence is as common as VTE after total knee arthroplasty.²⁸ While the understanding of the relative prognostic clinical significance of symptomatic versus asymptomatic VTE makes interpreting this difference difficult, these studies nonetheless demonstrate that the overall incidence of VTE after spine surgery is substantial.

Common risk factors for VTE after elective spine surgery include increasing age,^{18,29,30} coagulopathy,³¹ malignancy,³⁰ hypertension,³² reduced mobility or functional disability,³³⁻³⁵ and surgical factors, including length of surgery and blood loss.^{18,36-38} Hohl et al⁹ report a significant increase in symptomatic PEs (3%) in patients who underwent fusions of 5 or more segments. Jacobs et al³⁹ noted risk factors for VTE in spine trauma patients to be the result of prolonged operative time, reduced mobilization, and increased systemic inflammation. Piper et al,³⁶ in a NSQIP query of 22 434 patients who underwent any spine surgery, identified 13 predisposing factors for VTE, which included hypertension, an operative time of 4 hours or greater, American Society of Anesthesiologists classification of ≥ 3 , quadriplegia/paraplegia, and inpatient status. However, their work studied all-comers and included both inpatient/outpatient procedures and acute/elective indications.

VTE prophylaxis efficacy and safety studies are largely inconsistent, retrospective, and underpowered. A systematic review by Glotzbecker et al⁴⁰ found a 50% reduction in

symptomatic VTE when both compression stockings and pneumatic compression mechanoprophylaxis were employed following spine surgery in all-comers. In this broad population, pneumatic compression was equivalent to chemoprophylaxis in VTE risk reduction. Associations between VTE chemoprophylaxis modalities sporadically demonstrate an increased risk of bleeding, epidural hematoma, or wound drainage, are commonly underpowered to prove therapeutic efficacy, and rely on retrospective data. Cox et al,¹² determined that starting unfractionated heparin on the day of surgery in all-comers decreased the risk of VTE, although complications were not addressed. The risk of bleeding with unfractionated heparin was reported to be substantial. McLynn et al³⁴ in their NSQIP study reported that unfractionated heparin increased the relative risk of developing an operative hematoma by 7.37 times. Warfarin was similarly associated with increased perioperative blood loss, as preoperative dosing was required to achieve postoperative therapeutic effect.⁴¹ In contrast, this bleeding risk was not present in patients treated with low-molecular-weight heparin starting 36 hours after cervical or lumbar elective spine procedures.¹¹ Few prior works have evaluated “nontraditional” VTE prophylaxis methods, such as factor Xa inhibitors, in the elective spine population. However, a single prospective randomized trial by Du et al⁴² compared oral rivaroxaban and parnaparin started 6 to 8 hours after lumbar spine surgery for 14 days total. No difference was observed in risk reduction or complication between groups.

Limited literature has led to inconclusive consensus recommendations. The North American Spine Society cited a lack of high-quality studies regarding VTE prophylaxis after elective surgery, rendering an official recommendation that decisions regarding VTE prophylaxis be made on a patient-by-patient basis, balanced with a risk of postoperative bleeding that existing literature failed to demonstrate was outweighed by therapeutic efficacy.^{43,44}

The American College of Chest Physicians nearly universally recommended use of pneumatic compression devices following spine surgery. This included high-risk patients, despite the authors citing a lack of high-quality literature to support such recommendations.⁴⁵ Recommendations for postoperative spine VTE prophylaxis from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom included the use of mechanical thromboprophylaxis, with the addition of low-molecular-weight heparin for high-risk patients.⁴⁶ Individual works have proposed their own novel criteria for chemoprophylaxis. Eskildsen et al⁴⁷ proposed a point-based, 3-part criterion for VTE prophylaxis after spine surgery that considers patient, surgical, and bleeding risks. This algorithm reflects many of the same risk factors used as absolute criteria in our work, such as the use of estrogen-containing contraceptives, revision procedures, or multilevel interventions. Unique to their protocol was a score subtraction for high bleeding risk patients, which was not considered in our present study. The wide diversity of rendered opinions illustrates the importance of identifying an ideal therapy following major

spine surgery, particularly with respect to comorbid patients. However, it also exposes the shortcomings of existing works.

The selection of fondaparinux, an indirect, selective factor Xa inhibitor, was because of its convenience, once-a-day dosing and previously effective use in the arthroplasty population.⁴⁸ While the mechanism of action of fondaparinux does not significantly affect the coagulation cascade, it has no effect on platelets and has displayed the potential to prevent complications in patients with heparin-induced thrombocytopenia.⁴⁹ Concerns about major bleeding with fondaparinux therapy observed perioperatively after major abdominal surgeries⁵⁰ have largely not been borne out in the orthopedic literature when a dosing of 1.5 to 3.0 mg daily was employed.⁵¹ While a slight, nonsignificant increase in the risk of bleeding was noted, Venker et al⁵² in their meta-analysis comparing the efficacy and bleeding risks of newer anticoagulation modalities with enoxaparin in the total joint population found that fondaparinux was more effective than 30 mg twice-daily enoxaparin in reducing the risk of VTE. This agreed with a previous meta-analysis of 4 high-quality trials comparing fondaparinux and enoxaparin.¹³ Unlike traditional anticoagulation modalities, there was no dose- or time-dependent renal accumulation of a reduced fondaparinux dosing (1.5 mg daily) in patients with chronic kidney disease,⁵³ with outcomes equivalent to healthy patients receiving enoxaparin.⁵⁴ Starting fondaparinux on post-operative day 2 was largely based on surgeon preference, although it should be noted that premature dosing of fondaparinux <6 hours after surgery has been associated with an increased risk of major bleeding after abdominal surgery.⁵⁰

Limitations

While this study is a retrospective analysis of prospectively collected data, the choice of fondaparinux therapy for higher risk patients invites a clear potential for selection bias. While powered to detect differences between groups, the present study includes a small sample size of convenience that was not designed to establish causality between the use of fondaparinux and a reduction in the incidence of VTE.

The study was conducted at a tertiary referral center where complex spine surgery is routinely performed, thus conclusions may not be generalizable to the population at large, and external validation studies are required. Therapeutic length was not standardized, as fondaparinux was administered only during the inpatient stay. Inpatient mechanoprophylaxis and post-discharge aspirin was employed in all patients. The utility of fondaparinux reported in the present study must therefore be considered as a part of a larger multimodal VTE prophylaxis strategy. Length of fondaparinux therapy and time until transition to aspirin was dependent on the length of hospital stay.

Findings of this work must be validated through a high-quality randomized controlled trial before clinical recommendations can be rendered. This study in no way replaces a randomized controlled trial and makes no claims about the safety or efficacy of fondaparinux.

Conclusion

The addition of fondaparinux as inpatient VTE prophylaxis following elective spine surgeries in comorbid patients significantly decreased the incidence of VTE compared with post-discharge ASA alone. The use of fondaparinux was also not associated with an increased incidence of post-operative complications. While the potential of fondaparinux in this patient group is encouraging, high-quality multicenter trials are required to validate these findings.

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.

ORCID iD

Mitchell S. Fourman, MD, MPhil  <https://orcid.org/0000-0001-5886-546X>

References

1. Kwong LM, Kimball JA. Postorthopedic surgery joint replacement surgery venous thromboembolism prophylaxis. *Hematol Oncol Clin North Am.* 2016;30:1007-1018. doi:10.1016/j.hoc.2016.05.001
2. Yamanaka Y, Ito H. Incidence of venous thromboembolism in patients undergoing major hip surgeries at a single institution: a prospective study. *Open Orthop J.* 2016;10:252-257. doi:10.2174/1874325001610010252
3. Zhang ZH, Shen B, Yang J, et al. Risk factors for venous thromboembolism of total hip arthroplasty and total knee arthroplasty: a systematic review of evidences in ten years. *BMC Musculoskelet Disord.* 2015;16:24. doi:10.1186/s12891-015-0470-0
4. Zhang J, Chen Z, Zheng J, Breusch SJ, Tian J. Risk factors for venous thromboembolism after total hip and total knee arthroplasty: a meta-analysis. *Arch Orthop Trauma Surg.* 2015;135:759-772. doi:10.1007/s00402-015-2208-8
5. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database Syst Rev.* 2016;(3):CD004179. doi:10.1002/14651858.CD004179.pub2
6. Paydar S, Sabetian G, Khalili H, et al. Management of deep vein thrombosis (DVT) prophylaxis in trauma patients. *Bull Emerg Trauma.* 2016;4:1-7.
7. Takahashi H, Yokoyama Y, Iida Y, et al. Incidence of venous thromboembolism after spine surgery. *J Orthop Sci.* 2012;17:114-117. doi:10.1007/s00776-011-0188-2
8. Inoue H, Watanabe H, Okami H, Kimura A, Takeshita K. The rate of venous thromboembolism before and after spine surgery as determined with indirect multidetector CT. *JB JS Open Access.* 2018;3:e0015. doi:10.2106/jbjs.oe.18.00015

9. Hohl JB, Lee JY, Rayappa SP, et al. Prevalence of venous thromboembolic events after elective major thoracolumbar degenerative spine surgery. *J Spinal Disord Tech*. 2015;28:E310-E315. doi:10.1097/BSD.0b013e31828b7d82
10. Schoenfeld AJ, Herzog JP, Dunn JC, Bader JO, Belmont PJ Jr. Patient-based and surgical characteristics associated with the acute development of deep venous thrombosis and pulmonary embolism after spine surgery. *Spine (Phila Pa 1976)*. 2013;38:1892-1898. doi:10.1097/BRS.0b013e31829fc3a0
11. Strom RG, Frempong-Boadu AK. Low-molecular-weight heparin prophylaxis 24 to 36 hours after degenerative spine surgery: risk of hemorrhage and venous thromboembolism. *Spine (Phila Pa 1976)*. 2013;38:E1498-E1502. doi:10.1097/BRS.0b013e3182a4408d
12. Cox JB, Weaver KJ, Neal DW, Jacob RP, Hoh DJ. Decreased incidence of venous thromboembolism after spine surgery with early multimodal prophylaxis: clinical article. *J Neurosurg Spine*. 2014;21:677-684. doi:10.3171/2014.6.spine13447
13. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162:1833-1840.
14. Cafri G, Paxton EW, Chen Y, et al. Comparative effectiveness and safety of drug prophylaxis for prevention of venous thromboembolism after total knee arthroplasty. *J Arthroplasty*. 2017;32:3524-3528.e1. doi:10.1016/j.arth.2017.05.042
15. Agaba P, Kildow BJ, Dhotar H, Seyler TM, Bolognesi M. Comparison of postoperative complications after total hip arthroplasty among patients receiving aspirin, enoxaparin, warfarin, and factor Xa inhibitors. *J Orthop*. 2017;14:537-543. doi:10.1016/j.jor.2017.08.002
16. Chang CM, Yin WY, Wei CK, et al. Adjusted age-adjusted Charlson Comorbidity Index Score as a risk measure of perioperative mortality before cancer surgery. *PLoS One*. 2016;11:e0148076. doi:10.1371/journal.pone.0148076
17. Namboothiri S. Incidence of deep vein thrombosis after major spine surgeries with no mechanical or chemical prophylaxis. *Evid Based Spine Care J*. 2012;3:29-33. doi:10.1055/s-0032-1327807
18. Dhillon ES, Khanna R, Cloney M, et al. Timing and risks of chemoprophylaxis after spinal surgery: a single-center experience with 6869 consecutive patients. *J Neurosurg Spine*. 2017;27:681-693. doi:10.3171/2017.3.spine161076
19. Bryson DJ, Uzoigwe CE, Braybrooke J. Thromboprophylaxis in spinal surgery: a survey. *J Orthop Surg Res*. 2012;7:14. doi:10.1186/1749-799X-7-14
20. Ploumis A, Ponnappan RK, Sarbello J, et al. Thromboprophylaxis in traumatic and elective spinal surgery: analysis of questionnaire response and current practice of spine trauma surgeons. *Spine (Phila Pa 1976)*. 2010;35:323-329. doi:10.1097/BRS.0b013e3181ca652e
21. Glotzbecker MP, Bono CM, Harris MB, Brick G, Heary RF, Wood KB. Surgeon practices regarding postoperative thromboembolic prophylaxis after high-risk spinal surgery. *Spine (Phila Pa 1976)*. 2008;33:2915-2921. doi:10.1097/BRS.0b013e318190702a
22. Catre MG. Anticoagulation in spinal surgery. A critical review of the literature. *Can J Surg*. 1997;40:413-419.
23. Schizas C, Neumayer F, Kosmopoulos V. Incidence and management of pulmonary embolism following spinal surgery occurring while under chemical thromboprophylaxis. *Eur Spine J*. 2008;17:970-974. doi:10.1007/s00586-008-0668-z
24. Lee HM, Suk KS, Moon SH, Kim DJ, Wang JM, Kim NH. Deep vein thrombosis after major spinal surgery: incidence in an East Asian population. *Spine (Phila Pa 1976)*. 2000;25:1827-1830.
25. Ferree BA, Wright AM. Deep venous thrombosis following posterior lumbar spinal surgery. *Spine (Phila Pa 1976)*. 1993;18:1079-1082.
26. Sansone JM, del Rio AM, Anderson PA. The prevalence of and specific risk factors for venous thromboembolic disease following elective spine surgery. *J Bone Joint Surg Am*. 2010;92:304-313. doi:10.2106/jbjs.h.01815
27. Tominaga H, Setoguchi T, Tanabe F, et al. Risk factors for venous thromboembolism after spine surgery. *Medicine (Baltimore)*. 2015;94:e466. doi:10.1097/MD.0000000000000466
28. Migita K, Bito S, Nakamura M, et al. Venous thromboembolism after total joint arthroplasty: results from a Japanese multicenter cohort study. *Arthritis Res Ther*. 2014;16:R154. doi:10.1186/ar4616
29. Yoshioka K, Murakami H, Demura S, et al. Comparative study of the prevalence of venous thromboembolism after elective spinal surgery. *Orthopedics*. 2013;36:e223-e228. doi:10.3928/01477447-20130122-26
30. Akeda K, Matsunaga H, Imanishi T, et al. Prevalence and countermeasures for venous thromboembolic diseases associated with spinal surgery: a follow-up study of an institutional protocol in 209 patients. *Spine (Phila Pa 1976)*. 2014;39:791-797. doi:10.1097/brs.0000000000000295
31. Charen DA, Qian ET, Hutzler LH, Bosco JA. Risk factors for postoperative venous thromboembolism in orthopaedic spine surgery, hip arthroplasty, and knee arthroplasty patients. *Bull Hosp Jt Dis (2013)*. 2015;73:198-203.
32. Xin WQ, Xin QQ, Ming HL, et al. Predictable risk factors of spontaneous venous thromboembolism in patients undergoing spine surgery. *World Neurosurg*. 2019;127:451-463. doi:10.1016/j.wneu.2019.04.126
33. Kim HJ, Iyer S, Diebo BG, et al. Clinically significant thromboembolic disease in adult spinal deformity surgery: incidence and risk factors in 737 patients. *Global Spine J*. 2018;8:224-230. doi:10.1177/2192568217724781
34. McLynn RP, Diaz-Collado PJ, Ottesen TD, et al. Risk factors and pharmacologic prophylaxis for venous thromboembolism in elective spine surgery. *Spine J*. 2018;18:970-978. doi:10.1016/j.spinee.2017.10.013
35. Wang T, Yang SD, Huang WZ, Liu FY, Wang H, Ding WY. Factors predicting venous thromboembolism after spine surgery. *Medicine (Baltimore)*. 2016;95:e5776. doi:10.1097/md.00000000000005776
36. Piper K, Algattas H, DeAndrea-Lazarus IA, et al. Risk factors associated with venous thromboembolism in patients undergoing spine surgery. *J Neurosurg Spine*. 2017;26:90-96. doi:10.3171/2016.6.spine1656

37. Bekelis K, Desai A, Bakhoun SF, Missios S. A predictive model of complications after spine surgery: the National Surgical Quality Improvement Program (NSQIP) 2005-2010. *Spine J.* 2014;14:1247-1255. doi:10.1016/j.spinee.2013.08.009
38. Wang TY, Sakamoto JT, Nayar G, et al. Independent predictors of 30-day perioperative deep vein thrombosis in 1346 consecutive patients after spine surgery. *World Neurosurg.* 2015;84:1605-1612. doi:10.1016/j.wneu.2015.07.008
39. Jacobs LJ, Woods BI, Chen AF, Lunardini DJ, Hohl JB, Lee JY. Safety of thromboembolic chemoprophylaxis in spinal trauma patients requiring surgical stabilization. *Spine (Phila Pa 1976).* 2013;38:E1041-E1047. doi:10.1097/BRS.0b013e31829879cc
40. Glotzbecker MP, Bono CM, Wood KB, Harris MB. Thromboembolic disease in spinal surgery: a systematic review. *Spine (Phila Pa 1976).* 2009;34:291-303. doi:10.1097/BRS.0b013e318195601d
41. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. *Spine (Phila Pa 1976).* 1996;21:853-859.
42. Du W, Zhao C, Wang J, Liu J, Shen B, Zheng Y. Comparison of rivaroxaban and parnaparin for preventing venous thromboembolism after lumbar spine surgery. *J Orthop Surg Res.* 2015;10:78. doi:10.1186/s13018-015-0223-7
43. Bono CM, Watters WC 3rd, Heggeness MH, et al. An evidence-based clinical guideline for the use of antithrombotic therapies in spine surgery. *Spine J.* 2009;9:1046-1051. doi:10.1016/j.spinee.2009.09.005
44. Schuster JM, Fischer D, Dettori JR. Is chemical antithrombotic prophylaxis effective in elective thoracolumbar spine surgery? Results of a systematic review. *Evid Based Spine Care J.* 2010;1:40-45.
45. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e227S-e277S. doi:10.1378/chest.11-2297
46. Hill J, Treasure T. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance. *BMJ.* 2007;334:1053-1054. doi:10.1136/bmj.39174.678032.AD
47. Eskildsen SM, Moll S, Lim MR. An algorithmic approach to venous thromboembolism prophylaxis in spine surgery. *J Spinal Disord Tech.* 2015;28:275-281. doi:10.1097/bsd.0000000000000321
48. Turpie AG, Bauer KA, Eriksson BI, Lassen MR; PENTATHALON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet.* 2002;359:1721-1726. doi:10.1016/s0140-6736(02)08648-8
49. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Use of fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. *J Am Coll Cardiol.* 2017;70:2636-2648. doi:10.1016/j.jacc.2017.09.1099
50. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. *J Thromb Haemost.* 2007;5:1854-1861. doi:10.1111/j.1538-7836.2007.02657.x
51. Turpie AG, Gallus AS, Hoek JAPentasaccharide Investigators. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med.* 2001;344:619-625. doi:10.1056/nejm200103013440901
52. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: a meta-analysis. *J Arthroplasty.* 2017;32:645-652. doi:10.1016/j.arth.2016.09.033
53. Hester W, Fry C, Gonzalez D, Cohen-Wolkowicz M, Inman BA, Ortel TL. Thromboprophylaxis with fondaparinux in high-risk postoperative patients with renal insufficiency. *Thromb Res.* 2014;133:629-633. doi:10.1016/j.thromres.2013.11.019
54. Mismetti P, Samama CM, Rosencher N, et al. Venous thromboembolism prevention with fondaparinux 1.5 mg in renally impaired patients undergoing major orthopaedic surgery. A real-world, prospective, multicentre, cohort study. *Thromb Haemost.* 2012;107:1151-1160. doi:10.1160/th11-09-0640