

Thromboprophylaxis in Orthopedic Surgery: How Long Is Long Enough?

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Abstract

Pharmacologic thromboprophylaxis with low-molecular-weight heparins, vitamin K antagonists, or fondaparinux is well tolerated and effective in preventing venous thromboembolism (VTE) in major orthopedic surgery but is often limited to in-hospital use. However, 45% to 80% of all symptomatic VTE events occur after hospital discharge. Extended-duration VTE prophylaxis for 28 to 35 days reduces risk for late VTE by up to 70%.

In this article, I review the evidence supporting guideline recommendations regarding extended-duration prophylaxis after major orthopedic surgery and provide an overview of current and emerging literature regarding prevention of postoperative VTE in patients undergoing this surgery.

Patients undergoing major orthopedic surgery, including hip and knee arthroplasty and hip fracture surgery, are at high risk for developing postoperative venous thromboembolism (VTE). VTE can be classified as deep vein thrombosis (DVT) or pulmonary embolism (PE), and pharmacologic thromboprophylaxis is established as the standard of care for these patients.¹ Currently recommended prophylactic regimens for patients undergoing major orthopedic surgery include aspirin, low-molecular-weight heparins (LMWHs), the synthetic pentasaccharide fondaparinux, and adjusted-dose oral vitamin K antagonists (VKAs).¹⁻³

However, despite use of in-hospital prophylaxis in orthopedic patients, activation of coagulation pathways persists, and, therefore, the risk for VTE remains high for several months after hospital discharge.¹ As a consequence, the majority of symptomatic VTE events occur after patients leave the hospital setting.¹ Thromboprophylaxis is routinely administered to patients who have undergone orthopedic surgery, but it is often stopped at time of hospital discharge.^{1,4} Thus, patients are at continued risk for

developing symptomatic VTE and its complications after discharge from the hospital.⁵ Extended-duration prophylaxis with LMWH or VKA in elective hip or knee surgery, or with fondaparinux in hip fracture surgery, reduces the incidence of late thrombotic events.⁶⁻⁸

In this review, I discuss the importance of administering appropriate-duration thromboprophylaxis to reduce the incidence of thromboembolic complications after major orthopedic surgery.

RISK FACTORS FOR VTE IN MAJOR ORTHOPEDIC SURGERY

Major orthopedic surgery is a well-recognized risk factor for development of VTE.^{1,2} Surgical trauma (including vessel trauma and tissue injury), venous stasis during surgery and early postoperative care, and activation of the coagulation cascade all contribute to the risk for perioperative VTE.^{1,9,10} Furthermore, patients often have other factors (eg, advanced age, obesity, immobility) that might further increase the risk for VTE.¹

“We now know that the coagulation cascade remains activated for at least 5 to 6 weeks after major orthopedic surgery.^{9,13,14}”

Consequently, the incidence of VTE in the absence of prophylaxis ranges from 40% to 60% (venographic rates) 7 to 14 days after major orthopedic surgery.^{1,11} The rate of DVT during the same period is approximately 50% (Table I).^{1,2} A high incidence of PE is also found in orthopedic surgery patients who do not receive thromboprophylaxis. For example, one study using the medical records from almost 8,000 total hip arthroplasties (THAs) performed over a 12-year period found that fatal PE was the single leading cause of death, occurring in 1% of patients.¹²

DURATION OF VTE RISK

The natural history of VTE after major orthopedic surgery has become better defined in recent years. We now know that the coagulation cascade remains activated for at least 5 to 6 weeks after major orthopedic surgery.^{9,13,14} Furthermore, stopping antithrombotic prophylaxis a week after surgery allows a secondary surge in procoagulant activity.¹³ This can lead to asymptomatic DVT, which affects at least half of all

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patients but resolves spontaneously.¹ However, silent postoperative DVT combined with venous injury, impaired coagulation, and venous stasis caused by immobility can allow existing thrombi to propagate and new thrombi to develop.¹

Patients remain in a prothrombotic state, linked with a heightened risk for VTE, for several weeks after orthopedic surgery.^{11,15-20} This prolonged duration of VTE risk is reflected in the high rates of symptomatic VTE after discharge. Forty-five percent to 80% of all symptomatic VTE events after major orthopedic surgery occur after hospital discharge.^{1,11} One study found that more than 25% of patients with no evidence of DVT during hospital stay developed venographic DVT 6 weeks after discharge.¹⁷

VTE has been reported to occur up to 3 months after surgery in spite of in-hospital prophylaxis.¹ One large epidemiologic study reported the rates of VTE in more than 24,000 THA patients who received some form of thromboprophylaxis.¹¹ This study revealed that 76% of patients were diagnosed with VTE after hospital discharge. Diagnosis was made using pulmonary arteriography, lower extremity venography, vascular ultrasonography, ventilation-perfusion lung scan, or impedance plethysmography. Median time to VTE diagnosis after surgery was 17 days.

The protracted risk for VTE among orthopedic patients has also been noted in clinical studies of thromboprophylaxis. The Pentasaccharide in Hip-Fracture Surgery (PENTHIFRA) study assessed the effects of prophylaxis with fondaparinux or enoxaparin for 5 to 9 days in 1,711 patients.²⁰ Over a 5- to 7-week follow-up, there were 30 symptomatic VTE events and 15 fatal PEs. Most of the events, 22 symptomatic VTE events and 11 fatal PEs, occurred 11 to 49 days after patient discharge.

Reported rates of VTE events after discharge from hospital vary by type of orthopedic procedure, use of thromboprophylaxis, VTE assessment basis (objective or symptoms), and timing of follow-up. For example, in THA patients who received 15 days of prophylactic LMWH therapy, the rate of venographically confirmed DVT occurring within 12 to 14 days of surgery was approximately 20%.¹⁶ Another study investigated the rates of VTE in THA patients who received thromboprophylaxis until hospital discharge.¹⁵ Overall,

10.5% of patients who had no evidence of VTE during their hospital stay developed proximal DVT within the first 2 months after discharge.

The postoperative period of risk for VTE might also be related to type of orthopedic procedure. In a prospective study of 4,840 joint surgery patients, DVT symptoms appeared a mean of 27 days after THA and a mean of 17 days after total knee arthroplasty (TKA).¹⁹ Another study investigated use of extended-duration enoxaparin thromboprophylaxis after orthopedic surgery.²¹ All patients received enoxaparin 40 mg/d for 7 to 10 days and were then randomized to either enoxaparin 40 mg/d or placebo for another 3 weeks. Extending duration of prophylaxis reduced VTE rates in THA patients (23% with placebo, 8% with extended-duration prophylaxis) but not in TKA patients (21% with placebo, 18% with extended-duration prophylaxis). There were no significant differences in bleeding rates between treatment groups (2.5% with placebo, 2.3% with extended-duration enoxaparin; $P = .811$). These findings imply that the VTE risk associated with THA lasts longer than that associated with TKA.

In hip fracture cases, there is often a delay between injury and surgery. Therefore, the patient is already in a prothrombotic state at time of surgery, and the surgery increases the risk for VTE further. Accordingly, duration of VTE risk was longest after hip fracture surgery (mean time to symptomatic DVT, 36 days) than after all other orthopedic surgeries.¹⁹ A study of nursing home residents and community patients showed a decline in ambulatory status in both groups immediately after hip fracture surgery.²² A more recent study of VTE in nursing home residents demonstrated that immobility leads to increased risk for VTE.²³ Thus, a decline in ambulatory status might increase the risk for VTE.

Furthermore, type of additional medications (eg, anticoagulants) might also influence the period of VTE risk and whether surgical procedures should be delayed. For example, some evidence suggests that patients receiving clopidogrel should wait before undergoing orthopedic surgery, though the exact timing of the delay is controversial.²⁴

Table I. Incidence of Objectively Diagnosed Deep Vein Thrombosis (DVT) and Clinical Pulmonary Embolism (PE) in Major Orthopedic Surgery With No Thromboprophylaxis

Surgery	Studies (N)	Patients (N)	Incidence (%)	95% CI
DVT ^a				
Elective hip replacement	17	851	51	48-54
Total knee replacement	7	541	47	42-51
Hip fracture surgery	15	805	44	40-47
Clinical PE				
Elective hip replacement	25	1436	4	3-5.1
Traumatic surgery	11	494	6.9	4.8-9.5
Fatal PE				
Elective hip replacement	12	485	1.7	0.38-2.7
Traumatic surgery	23	1195	4	3-5.3

Abbreviation: CI, confidence interval.

^aIncidence is weighted mean.

Data from Cardiovascular Disease Educational and Research Trust.²

PHARMACOLOGIC PROPHYLAXIS IN ORTHOPEDIC SURGERY

Appropriate pharmacologic thromboprophylaxis can significantly reduce the risk for VTE in THA, TKA, and hip fracture surgery patients.^{1,2,25,26} The guidelines of the American College of Chest Physicians (ACCP)¹ and International Union of Angiology (IUA)² have helped define “appropriate prophylaxis” for patients undergoing major orthopedic surgery. Appropriate prophylaxis consists of selecting the appropriate agent at the appropriate dose for the appropriate duration according to the patient’s risk profile.

“One study found that more than 25% of patients with no evidence of DVT during hospital stay developed venographic DVT 6 weeks after discharge.^{17”}

The current clinical guidelines on VTE prevention recommend LMWHs and fondaparinux and VKAs as thromboprophylactic agents suitable for use as anticoagulants in orthopedic patients.¹⁻³ VKAs are widely used in North America for THA and TKA¹ but are not the favored therapy for these indications in Europe.² Current guidelines note that there is limited evidence regarding efficacy and safety of VKAs in hip fracture surgery.¹

A strong evidence base has shown that LMWHs are more effective than unfractionated heparin and VKAs across orthopedic surgical prophylaxis indications.^{1,27-30} Compared with placebo, LMWHs (nadroparin, certoparin) also significantly reduce DVT incidence in patients with plaster casts.^{31,32} The pentasaccharide fondaparinux has been proved effective in reducing VTE complications after major elective and emergency orthopedic surgery.^{1,20,33-35} However, the increased efficacy of fondaparinux in preventing postoperative VTE is associated with an increased rate of bleeding in comparison with LMWH prophylaxis. For example, Bauer and colleagues³³ found major bleeding in 11 patients treated with fondaparinux but in only 1

patient treated with enoxaparin; the difference was statistically significant ($P = .006$). However, in a study comparing fondaparinux with enoxaparin for prevention of VTE after hip fracture surgery, there were no significant differences between the groups in incidence of major bleeding (2.2% and 2.3%, respectively) or death from any cause (1.3% and 1.9%, respectively).²⁰

Current ACCP guidelines do not recommend use of only aspirin for VTE prophylaxis after orthopedic surgery.¹ However, the guidelines of the American Association of Orthopedic Surgeons (AAOS) recommend use of aspirin 325 mg twice daily as a prophylactic option for THA or TKA patients at increased risk for major bleeding and at standard or increased risk for PE.³

Oral anticoagulants in clinical development include the direct factor Xa inhibitor rivaroxaban (BAY 59-7939) and the direct thrombin inhibitor dabigatran etexilate. Early phase II and III studies have shown that these agents demonstrate efficacy and safety when used as thromboprophylaxis in THA and TKA.³⁶⁻⁴⁰ In THA patients, the rate of the composite endpoint of any DVT, PE, and all-cause mortality were 22%, 24%, 20%, 10%, 17% and 15% in patients receiving rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg twice daily and 30 mg once daily (starting 6 to 8 hours after surgery), respectively, and 17% in patients receiving enoxaparin 40 mg the evening before surgery and once daily thereafter ($P = .0504$).³⁹ The rates of major postoperative bleeding were 0% with rivaroxaban 2.5 mg, 2.5% with 5 mg, 2.9% with 10 mg, 6.5% with 20 mg, 10.8% with 30 mg twice daily, and 4.5% with 30 mg once daily ($P = .0008$). There were no bleeding events with enoxaparin.

In patients undergoing elective TKA, rivaroxaban was started 6 to 8 hours after surgery.⁴⁰ The rates of the composite endpoint of any DVT, PE, and all-cause mortality were 32%, 40%, 23%, 35%, and 25% for twice-daily rivaroxaban doses of 2.5 mg, 5 mg, 10 mg, 20 mg, and 30 mg, respectively ($P = .29$ for dose comparisons). The corresponding rate of the composite primary endpoint with enoxaparin 30 mg twice daily (started 12 to 24 hours after surgery) was 44%, and there was no significant difference in incidence of bleeding between any of the rivaroxaban dosage groups and enoxaparin.

Table II. Meta-Analyses^{6,7,49,50} Show Extended-Duration Venous Thromboembolism (VTE) Thromboprophylaxis Reduces Risk for VTE (Rates of Symptomatic VTE) Up to 3 Months After Surgery

Source	Studies (N)	Surgery	LMWH, n/N (%)	Placebo, n/N (%)	OR (95% CI)	NNT
^a Eikelboom et al ⁶	9	THA/TKA	25/1964 ^a (1.3)	58/1744 (3.3)	0.38 (0.24-0.61)	50
Hull et al ⁷	6	THA	15/1091 (1.4)	36/862 (4.2)	0.36 ^b (0.20-0.67)	NA
Cohen et al ⁴⁹	6	THA/TKA	22/1376 (1.6)	39/1192 (3.3)	0.50 (0.30-0.83)	NA
O'Donnell et al ⁵⁰	2	THA	5/465 (1.1)	12/442 (2.7)	0.39 (0.14-1.11)	64

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty; LMWH, low-molecular-weight heparin; OR, odds ratio; CI, confidence interval; NNT, number needed to treat; NA, not available.

^aData included 1 study with unfractionated heparin and 1 study with oral anticoagulant.

^bData presented as relative risk with 95% CI.

Table III. Postdischarge Incidence of VTE Events per 10,000 THAs and NNT to Prevent 1 Event in Patients Receiving Aspirin, LMWH/VKA, or Fondaparinux as Extended-Duration Prophylaxis Versus Control/Standard-Duration Prophylaxis

VTE	Control (n)	n (NNT)		
		Aspirin	LMWH/VKA	Fondaparinux
DVT/PE	240	160 (125)	80 (62)	24 (46)
PE	60	40 (500)	20 (250)	6 (185)
Fatal PE	6	4 (5000)	2 (2500)	0.6 (1850)

Abbreviations: VTE, venous thromboembolism; THA, total hip arthroplasty; NNT, number needed to treat; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; DVT, deep vein thrombosis; PE, pulmonary embolism.⁵²
Reproduced with permission from Kearon.⁵²

Another study investigated the efficacy and safety of once-daily dabigatran 150 mg or 220 mg compared with enoxaparin 40 mg once daily in THA patients.³⁸ The rates of the composite endpoint of any VTE and all-cause mortality were 8.6% and 6.0% in the dabigatran 150 mg and 220 mg groups, respectively, and 6.7% in the enoxaparin group (noninferiority demonstrated). There was no significant difference in major bleeding rates between dabigatran at either dose and enoxaparin ($P = .60$ for dabigatran 150 mg, and $P = .44$ for dabigatran 220 mg, both vs enoxaparin).

Overall, these studies showed that, for THA and TKA patients, the efficacy-and-safety profiles of rivaroxaban and dabigatran were similar to the profile of the LMWH enoxaparin.³⁶⁻⁴⁰ However, the complete clinical and safety profiles, and the application of these new oral agents for VTE prevention, are still to be determined.

BENEFITS OF EXTENDED-DURATION PROPHYLAXIS

Knee Arthroscopy

Randomized, controlled studies of knee arthroscopy have demonstrated the benefits of LMWH prophylaxis over no prophylaxis, placebo, and graduated compression stockings.⁴¹⁻⁴⁴ However, much more research is needed to determine whether benefits in terms of reduced VTE incidence outweigh the potential bleeding risks and costs. ACCP guidelines recommend early mobilization, but no other form of thromboprophylaxis, for knee arthroscopy patients who have no additional VTE risk factors; for patients with additional risk factors, LMWH prophylaxis is recommended.¹

Hip or Knee Arthroplasty

Several key clinical trials with the LMWHs enoxaparin^{21,45,46} and dalteparin^{18,47} have demonstrated that extended-duration postdischarge prophylaxis reduces relative incidence of VTE by 54% to 66% in hip surgery patients. For example, an early study of 179 THA patients compared placebo and prophylaxis with enoxaparin 40 mg once daily continued for another 21 days after discharge.⁴⁵ All patients received enoxaparin while in hospital for 13 to 15 days after surgery, and none had venographic DVT at hospital discharge. The rate of venographic DVT 21 days after discharge was significantly lower in the patients who received extended-duration prophylaxis compared with the patients

who received placebo (7.1% and 19.3%, respectively; $P = .018$). There were no major bleeding events in either group. Three patients who received enoxaparin (vs none who received placebo) experienced minor bleeding events. In another study, involving 262 THA patients, enoxaparin prophylaxis was extended for a total of 1 month (inpatient plus outpatient use).⁴⁶ The incidence of VTE was 39% in the placebo group and 18% in the extended-duration prophylaxis group ($P < .001$). As an indication of safety, 6 patients who received extended-duration prophylaxis and 1 patient who received placebo developed a hematoma at the injection site. In a hip replacement study, all 308 patients received initial in-hospital prophylaxis with dalteparin for 7 days before being randomized to receive either dalteparin or placebo for another 28 days.¹⁸ Extended-duration prophylaxis with dalteparin was associated with reduced incidence of DVT over the extension phase compared with placebo (11.8% and 25.8%, respectively; $P = .017$), and similar rates of hematoma at the injection site were found (1 patient in each group). A study of 281 THA patients also found that extending LMWH prophylaxis with dalteparin from 7 days to 35 days more than halved the risk for VTE, reducing the rate of DVT from 11.8% (95% confidence interval [CI], 6-20) to 4.4% (95% CI, 1-10; $P = .039$).⁴⁷ Although 1 patient in the placebo group experienced major bleeding, minor bleeding events and other adverse events were similar between the 2 groups.

Reduced VTE incidence with extended-duration thromboprophylaxis directly translates into reduced mortality rates.⁴⁸ A case-control study investigated the mortality outcomes in 179 hip fracture patients given antithrombotic therapy after discharge and 179 age- and sex-matched controls who did not receive any prophylaxis. Ninety-day VTE-associated mortality was lower in the patients who received prophylaxis (1.1%) than in those who did not (6.7%). This corresponds to an odds ratio (OR) of 0.17 (95% CI, 0.03-0.73) and was therefore a statistically significant finding ($P = .011$).⁴⁸

Several meta-analyses have confirmed the benefits of extended-duration prophylaxis with LMWHs in both THA and TKA populations (Table II).^{6,7,49,50} Overall, prophylaxis with LMWH for 4 weeks reduces the relative risk for VTE complications by up to 65% (Table II). Extended-duration prophylaxis also results in significantly lower rates of silent VTE. For example, the meta-analysis by Eikelboom and

Table IV. Comparison of 2008 ACCP,¹ 2006 IUA,² and 2007 AAOS³ Guidelines Regarding Prophylaxis Duration in Total Hip Arthroplasty, Total Knee Arthroplasty, and Hip Fracture Surgery

Guideline	Total Hip Arthroplasty	Total Knee Arthroplasty	Hip Fracture Surgery
2008 ACCP ^a	Extend LMWH (grade 1A), VKA (grade 1B), or fondaparinux (grade 1C) up to 35 days (grade 1A)	Extend LMWH (grade 1C), VKA (grade 1C), or fondaparinux (grade 1C) up to 35 days (grade 1C)	Extend fondaparinux (grade 1A), LMWH (grade 1C), or VKA (grade 1C) up to 35 days (grade 1A)
2006 IUA	Continue prophylaxis with LMWH (grade A) or fondaparinux (grade C) for 4-6 weeks	No extension recommended	No extension recommended
2007 AAOS ^b	Standard risk PE and bleeding: aspirin 325 mg twice daily for 6 weeks or LMWH for 7-12 days, or fondaparinux for 7-12 days or VKA (INR goal, ≤ 2.0) for 2-6 weeks	Standard risk PE and bleeding: aspirin 325 mg twice daily for 6 weeks or LMWH for 7-12 days, or fondaparinux for 7-12 days or VKA (INR goal, ≤ 2.0) for 2-6 weeks	Not included in guidelines

Abbreviations: ACCP, American College of Chest Physicians; IUA, International Union of Angiology; AAOS, American Association of Orthopedic Surgeons; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; PE, pulmonary embolism; INR, international normalized ratio.

^aFor total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, all patients should receive high-dose LMWH, or 2.5 mg fondaparinux or VKA to target INR of 2.5 for at least 10 days (all grade 1A).

^bPatients graded according to PE risk and bleeding risk. In patients with elevated risk for PE and standard risk for bleeding, aspirin is not recommended. In patients at standard or elevated risk for PE and elevated risk for bleeding, LMWH and fondaparinux are not recommended.

colleagues,⁶ which included both THAs and TKAs, noted that asymptomatic, venographically detected DVT was 19.6% in control subjects versus 9.6% in patients given extended-duration prophylaxis (OR, 0.48; 95% CI, 0.36-0.63).

Furthermore, extended-duration prophylaxis with enoxaparin or dalteparin appears not to be associated with an increase in the rate of major bleeding.⁶ In the 9-study meta-analysis, the rate of major bleeding was 0.3% in the combined placebo and untreated control group compared with 0.1% in the extended-duration prophylaxis group. The incidence of minor bleeding was higher in the extended-duration prophylaxis group (3.7%) than in the untreated control group (2.5%; OR, 1.56; 95% CI, 1.08-2.26).⁶

Meta-analyses provide a valuable overview of available datasets and identify trends across similar studies, but they too have their limitations. Some meta-analyses of extended-duration prophylaxis included unblinded studies and the pooling of data from studies with different designs, which provide only a retrospective approximation of individual study findings. Nonetheless, the findings of meta-analyses do reflect the results of prospective clinical investigations and support the clinical benefit of extending the duration of prophylaxis in order to reduce the burden of postoperative VTE associated with major orthopedic surgery.

The meta-analysis by Eikelboom and colleagues⁶ also reported a larger reduction in risk for VTE after extended-duration prophylaxis among THA patients (risk reduction, 67%) than among TKA patients (risk reduction, 29%). Similar results were reported in a study comparing extended-duration prophylaxis with standard-duration in-hospital prophylaxis with the LMWH enoxaparin in 435 THA and 438 TKA patients.²¹ After receiving in-hospital LMWH prophylaxis for 7 to 10 days, patients were randomly assigned to placebo or to another 3 weeks of outpatient LMWH treatment. Although extended-duration prophylaxis significantly

reduced the rate of objectively confirmed VTE from 23.2% to 8.0% in THA patients, the rates of VTE for TKA patients were similar between the placebo and extended-duration groups (20.8% and 17.5%, respectively).²¹ These findings suggest that extended-duration prophylaxis benefits THA patients more than TKA patients.

VKAs also significantly reduce the risk for postoperative VTE when used as extended-duration outpatient prophylaxis.⁵¹ In one study, THA patients were randomized to receive either VKA for the duration of their inpatient stay ($n = 176$) or VKA for another 4 weeks after discharge ($n = 184$). The rate of objectively confirmed VTE after 3 months was 5.1% in control subjects and 0.5% in patients given extended-duration VKA prophylaxis. There was only 1 case of major bleeding in the extended-duration prophylaxis group.⁵¹

Debate continues over the ideal duration of extended prophylaxis in at-risk groups. ACCP guidelines recommend that THA, TKA, and hip fracture surgery patients be given thromboprophylaxis for at least 10 days.¹ AAOS guidelines do not recommend extended-duration prophylaxis with LMWH or fondaparinux but indicate that VKA and aspirin can be continued for 6 weeks.³ This might reflect the view that, though the data suggest extended-duration prophylaxis can significantly reduce the risk for postoperative VTE, the absolute number of VTE events prevented is low. The number needed to treat to prevent 1 VTE event after THA, using different antithrombotic agents, is outlined in Table III.⁵² These data provide indirect, estimated comparisons of available antithrombotic agents for extended-duration prophylaxis.

Hip Fracture Surgery

Hip fracture surgery patients are at highest risk for VTE.^{1,2} Their rates of DVT are 40% to 60%, and 3% to 11% of these patients are at risk for postoperative PE when prophylaxis is not used.¹

A study involving 897 patients demonstrated that 5 weeks of prophylaxis with the LMWH enoxaparin 40 mg/d can reduce the rate of postoperative VTE after hip fracture surgery.⁵³ Clinical signs of DVT were reported in 4.2% of cases, with a diagnosis confirmed in just 0.6%, and clinical PE was confirmed in 0.2% of cases. The rate of major bleeding complications was 4.7%.

The PENTHIFRA-Plus study of 656 hip fracture surgery patients showed that fondaparinux prophylaxis extended for 3 weeks can reduce the risk for postoperative VTE.⁸ In this trial, all patients received fondaparinux in hospital for 6 to 8 days, after which they were randomized to receive either placebo or fondaparinux for another 19 to 23 days. The rate of symptomatic VTE was reduced from 2.7% to 0.3% with extended-duration prophylaxis, but there was an accompanying increase in major bleeding events in the fondaparinux group compared with the placebo group (2.4% and 0.6%, respectively), though this difference was not statistically significant ($P = .06$).⁸ Guideline recommendations for prophylaxis with fondaparinux in hip arthroplasty were extrapolated from this study.^{1,2}

GUIDELINE RECOMMENDATIONS: DURATION OF PROPHYLAXIS

As already mentioned, there is no consensus regarding optimal duration of VTE prophylaxis in major orthopedic surgery. Nevertheless, over successive ACCP guideline updates (since 1998), appropriate duration of prophylaxis for patients undergoing this surgery has lengthened, reflecting the increasing evidence favoring extended-duration antithrombotic therapy.^{1,54-56}

For both THA and TKA, the 1998 and 2001 ACCP guidelines recommended a 7- to 10-day period of prophylaxis coinciding with length of hospital stay (grade 1A recommendation).^{54,55} Between 2001 and 2004, the ACCP revised its recommendations: High-risk patients should receive out-of-hospital LMWH prophylaxis for 28 to 35 days (grade 1A), but this recommendation did not include TKA patients.⁵⁶ Specific guidelines concerning duration of prophylaxis in hip fracture surgery were not introduced until 2004, when the recommendation was prophylaxis for at least 10 days (grade 1A), with extended duration of 28 to 35 days (grade 1A).⁵⁶ The 2008 ACCP guidelines now recommend that both THA and hip fracture surgery patients receive up to 35 days (grade 1A) of prophylaxis with LMWH, VKA, or fondaparinux. There is also a recommendation (grade 2B) that TKA patients receive prophylaxis for a period of up to 35 days.¹

Other clinical guidelines also support the need for appropriate-length prophylaxis in orthopedic patients. For example, IUA guidelines recommended that prophylaxis with LMWH (grade A) or fondaparinux (grade C) be continued for 4 to 6 weeks after THA.² Recently, the AAOS published guidelines on preventing symptomatic PE after orthopedic surgery. For THA and TKA patients at standard risk for PE and standard risk for major bleeding, these guidelines indicate that appropriate prophylaxis is 6 weeks

of aspirin, 7 to 12 days of LMWH or fondaparinux, or 2 to 6 weeks of VKA.³

Table IV compares the current recommendations from the ACCP, IUA, and AAOS guidelines. These guidelines differ in several ways, and there are many possible reasons for the discrepancies. Most notably, the AAOS guidelines focus exclusively on preventing symptomatic PE, which has a low incidence rate. Had the AAOS guidelines been broadened to cover clinical DVT events, they might be more aligned with the ACCP and IUA guidelines. Furthermore, the AAOS guidelines concern THA and TKA, not surgeries for traumatic injuries, such as hip fractures. The AAOS recommendations balance patient risk for PE and their risk for bleeding, as well as risk for bleeding associated with anticoagulant therapy. Accordingly, in a patient at elevated risk for PE but standard risk for bleeding, LMWH or fondaparinux is preferred over aspirin, but, when risk for bleeding exceeds risk for PE, aspirin is preferred over LMWH or fondaparinux.³ Guideline differences also result from considering various endpoints and treatment protocols specific to their fields of interest. For instance, the international normalized ratio values acceptable in orthopedics (<2) differ from those acceptable in other patient groups included within the ACCP and IUA guidelines for VTE prevention. Nevertheless, all the guidelines agree that thromboprophylaxis benefits patients undergoing orthopedic surgery.

However, publication of guidelines is insufficient. Prevention of thromboembolism requires that guidelines be implemented effectively and adopted by administering clinicians.⁵⁷

CONCLUSIONS

Patients undergoing major orthopedic surgery are at high risk for VTE. With the traumatic nature of the surgery and the prolonged period of reduced mobility after surgery, most patients remain at increased risk for DVT and PE for up to 3 months after surgical intervention. Perioperative thromboprophylaxis with VKA, the LMWHs enoxaparin or dalteparin, or fondaparinux prophylaxis for 7 to 10 days, has been proved to reduce the in-hospital incidence of VTE, but it does not prevent postdischarge VTE. Extended-duration pharmacologic prophylaxis—use of LMWH, VKA, or fondaparinux for 28 to 35 days—can significantly reduce the risk for late symptomatic VTE and thereby improve outcomes for patients after THA or hip fracture surgery. Discrepancies between ACCP, IUA, and AAOS recommendations as to optimal duration of thromboprophylaxis for patients undergoing major orthopedic surgery arise from differences in these organizations' objectives. Nevertheless, there is sound clinical evidence supporting use of extended-duration thromboprophylaxis in patients undergoing major orthopedic surgery.

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