ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: When should prophylactic anticoagulation begin after a hip fracture?

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A: The short answer is *immediately*, but several issues need consideration before starting pharmacologic prophylaxis for venous thromboembolism (VTE) in patients with a hip fracture:

- When is the patient scheduled for surgery?
- Which anticoagulant drug should be used?
- Which type of anesthesia is planned and how does that affect the choice of anticoagulant?
- How soon after surgery should anticoagulation be restarted, and for how long should it continue?

HIGH RISK OF DEATH

The question of when to start prophylactic anticoagulation after hip fracture is an important one, given the increasing incidence of hip fracture in the United States. Approximately 350,000 hip fractures occur annually,[1] with an anticipated increase to 500,000 by 2040.[2] Death rates of 4% to 6% during hospitalization[3] and 14% to 36% at 1 year[4] are notably higher than the 1% to 1.3% for patients undergoing total hip or knee replacements.[5]

Most hip fractures are treated surgically, and the American College of Chest Physicians (ACCP) puts hip fracture surgery in the highest risk category for VTE.[6] Prospective randomized controlled trials have shown that without prophylaxis the rate of deep vein thrombosis (DVT) in patients with hip fracture ranges from 46% to 75% using venography.[7–11] A British study looking at 580 consecutive patients with femoral neck fractures reported fatal pulmonary embolism in 4% of patients not receiving prophylaxis.[12] Clearly, all patients with hip fracture need prophylaxis against VTE.

THE DANGERS OF DELAY

We feel it is important to begin preventive anticoagulation immediately, since in many cases patients do not undergo surgery until 24 to 48 hours after arrival at the hospital, leaving them unprotected against the risks of VTE during that time. In addition, most hip fracture patients are elderly (average age 80 to 82[3,13,14]), and most require some degree of preoperative evaluation and medical stabilization before they go to the operating room.

Delay in presentation to the hospital after hip fracture and delay in time to surgery are associated with a significantly increased risk of DVT. One study showed that the incidence of DVT in patients who did not present to the hospital until more than 48 hours after hip fracture was 55%, compared with 6% in those presenting sooner than 48 hours ($P < .001$).[15] In another study[16] of 61 consecutive patients admitted for hip fracture, 62% of those who waited to undergo surgery at least 48 hours after hospital admission had preoperative venographic evidence of DVT.

These studies imply that the risk of VTE in hip fracture patients starts at the time of injury rather than after surgical repair, although one may argue that this reflects the increased underlying comorbidity in those in whom surgery is delayed.

Without prophylaxis 46% to 75% of hip fracture patients develop DVT

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OPTIONS FOR PROPHYLAXIS

VTE prophylaxis can be broadly classified in two categories: mechanical and pharmacologic.

Mechanical prevention

Mechanical VTE prophylaxis includes intermittent pneumatic compression (IPC) devices, graded compression stockings, and venous foot pumps. Studies of mechanical thromboprophylaxis in hip fracture patients are few, but a Canadian prospective randomized study[17] of the effectiveness of IPC devices in 231 patients with hip fractures found a DVT rate of 12% in the control group vs 4% in the group using IPC devices—a statistically significant difference.

Although these devices appear to be helpful, particularly when anticoagulation therapy is contraindicated, no randomized controlled trials have compared IPC devices with other methods of thromboprophylaxis in hip fracture patients.

Pharmacologic prevention

Patients are at risk of VTE while they wait 24–48 hours or more for surgery

Aspirin. Antiplatelet agents such as aspirin have been studied for their potential role in reducing VTE rates in patients with hip fracture. In the Pulmonary Embolism Prevention (PEP) trial, 13,356 patients who underwent surgery for hip fracture were randomized to receive either aspirin 160 mg daily or placebo, starting preoperatively and continuing for 35 days postoperatively.[18] Additional forms of thromboprophylaxis were used if the treating physician deemed it necessary, and these included low-dose unfractionated heparin in 18% of patients, low-molecular-weight heparin in 26%, and graded compression stockings in 30%. The use of aspirin reduced the incidence of DVT by 29% (P = .03) and pulmonary embolism by 43% (P = .002), despite a small but statistically significant increase in the risk of gastrointestinal and wound-related bleeding.

The PEP trial results come with a caveat, however, as a subgroup analysis of patients who also received low-molecular-weight heparin showed no statistically significant difference between aspirin and placebo in the rate of symptomatic VTE.

Warfarin. Trials of thromboprophylaxis using the vitamin K antagonist warfarin are limited in hip fracture patients. The largest was a prospective randomized controlled trial of 194 hip fracture patients who received aspirin 650 mg twice daily, or warfarin titrated to an international normalized tatio (INR) goal of 2.0 to 2.7, or placebo.[9] Prophylaxis began immediately after surgery and continued for 21 days or until hospital discharge. Venographic evidence of VTE was found in 20% of the warfarin group, 41% of the aspirin group, and 46% of the placebo group (P = .005). The incidence of proximal DVT or pulmonary embolism or both was 9% with warfarin, 11% with aspirin, and 30% with placebo (P = .001). There were no significant differences with respect to adverse bleeding outcomes among the three groups. This trial, in addition to two others comparing warfarin to placebo, shows relative risk reductions of over 60%.[9,19,20]

Heparins. Only a few trials have compared the effectiveness of low-dose unfractionated heparin with other agents for VTE prophylaxis in hip fracture patients. One prospective, double-blind, randomized controlled trial compared 90 hip fracture patients who received either low-dose unfractionated heparin (5,000 U every 8 hours) or the low-molecular-weight heparin dalteparin (5,000 U daily).[21] Venography showed DVT in 14% of patients on unfractionated heparin and in 32% of those taking dalteparin. Also, 14% of patients taking dalteparin had a lung scan with a high probability of pulmonary embolism, whereas none of those taking unfractionated heparin did. Both of these findings were statistically significant. No significant difference was observed with respect to bleeding complications.

In a randomized controlled study of the effects of dalteparin vs placebo on DVT in 82 hip fracture patients,[22] no difference in bleeding events was seen; however, dalteparin 5,000 U daily resulted in a statistically significant 50% decrease in the incidence of DVT.

A study of enoxaparin vs dalteparin in 197 hip fracture patients[23] found no significant difference in the frequency of DVT or bleeding complications.

Fondaparinux. The Pentasaccharide in Hip-Fracture Surgery study (PENTHIFRA)[24]

compared fondaparinux, a synthetic inhibitor of factor Xa, with enoxaparin. This large multicenter, randomized, double-blind trial of 1,711 hip fracture patients excluded patients if an epidural catheter was planned for more than 6 hours postoperatively, if the patient had surgery more than 48 hours from the time of admission, or if the serum creatinine level was greater than 2 mg/dL. Fondaparinux 2.5 mg daily subcutaneously was started 6 to 8 hours after surgery, and the second dose was given at least 12 hours after the first to prevent VTE, while enoxaparin 40 mg subcutaneously was begun on average 12 hours before surgery and restarted 12 to 24 hours after surgery. Despite no differences in clinically relevant bleeding rates, the incidence of total VTE was significantly lower in the fondaparinux group (8% vs 19%, $P < .001$).

ANTICOAGULATION AND NEUROAXIAL BLOCKADE

If the first dose of anticoagulant is given immediately on presentation, how does this influence the timing of surgery?

Aspirin is not recommended for VTE prophylaxis

This largely depends on which pharmacologic agent is used. An agent with a short half-life, such as low-dose unfractionated heparin 5,000 U, would allow hip fracture surgery to be performed safely under neuroaxial blockade (spinal or epidural anesthesia) after 6 to 8 hours without increasing the risk of epidural hematoma. If a prophylactic dose of a low-molecular-weight heparin such as dalteparin or enoxaparin is used, the surgery could be performed safely as early as 12 hours after the dose is given.

With fondaparinux, however, it may *not* be safe to proceed under neuroaxial blockade, even at 24 hours, as it has a half-life of 18 hours. In PENTHIFRA,[24] no patients received neuroaxial blockade after receiving fondaparinux preoperatively. We have neither the data nor a consensus recommendation to guide the preoperative timing of fondaparinux if neuroaxial blockade is planned.

Exactly when to restart anticoagulation after surgery is an important issue as well. The current American Society of Regional Anesthesia (ASRA) guidelines provide no guidance with regard to fondaparinux dosing, but common sense dictates waiting at least 6 hours after surgery to restart it, as was done in PENTHIFRA.[24] The ASRA guidelines do, however, allow once-daily prophylactic use of low-molecular-weight heparin in patients with an epidural catheter, but they recommend not removing the catheter until 12 hours after the heparin dose is given. And once the catheter is pulled, one must wait 2 hours to give another dose of heparin.[25]

DURATION OF PROPHYLAXIS

The duration of anticoagulation in hip fracture patients was addressed in a study called PENTHIFRA-PLUS.[26] In this multicenter double-blind trial, 656 patients undergoing hip fracture surgery were randomly assigned to receive a once-daily subcutaneous injection of either fondaparinux 2.5 mg or placebo for 19 to 23 days. Before randomization, all patients had received fondaparinux for 6 to 8 days postoperatively. Using bilateral venography, the total incidence of VTE was 35.0% in the placebo group but only 1.4% in the fondaparinux group, with a relative reduction in risk of 95.9% (95% confidence interval 87.2%–99.7%; $P < .001$). There was a trend toward increased major bleeding in the fondaparinux group compared with the placebo group ($P = .06$); however, there were no differences in the incidence of clinically relevant bleeding leading to death, reoperation, or critical organ bleeding. This study supports extended prophylaxis with fondaparinux for a total of 4 weeks after hip fracture surgery.

COST-EFFECTIVENESS OF ANTICOAGULATION

An analysis of cost-effectiveness that used efficacy and safety data from a clinical trial comparing fondaparinux and enoxaparin as VTE prophylaxis showed that enoxaparin offers advantages over fondaparinux when given for 7 days postoperatively in hip fracture patients.[27] Sensitivity analyses supported this finding at the lower extreme of VTE events; however, fondaparinux provided cost savings at the upper extreme. Cost per death averted and cost per life-year gained were similar for these two agents in these patients.

TABLE 1

Drugs and devices to prevent thromboembolism after hip fracture: An evidence-based comparison

	RECOMMENDED DOSING	DURATION	LEVEL OF EVIDENCE*	AMERICAN COLLEGE OF CHEST PHYSICIANS' OPINION
Fondaparinux	2.5 mg/day Start 6–8 hours after surgery	28 days	1A	Recommended
Aspirin	160 mg/day orally Start preoperatively	35 days	1A	Not recommended
Low-dose unfractionated heparin	5,000 U three times daily, subcutaneously Start preoperatively	9 days or until hospital discharge	1B	Recommended
Low-molecular-weight heparin				
Dalteparin	5,000 U daily Start preoperatively, up to 2 hours before surgery, but may lead to more bleeding after surgery	9 days or until hospital discharge	1C+	Recommended
Enoxaparin	40 mg daily Start up to 12 hours before surgery	28 days	1C+	Recommended
Warfarin	Start immediately after surgery	21 days or until hospital discharge	2B	Adjust dose to an international normalized ratio of 2.5
Intermittent pneumatic compression devices	Literature supports use before and after surgery May be used along with drug prophylaxis, but there is no evidence that this is superior to drug therapy alone	Upon admission and until hospital discharge	1C	Use only if anticoagulant drug therapy is contraindicated

*Level of evidence scale: 1, strong evidence; 2, weak evidence; A, consistent results from randomized controlled trials (RCTs); B, inconsistent results from RCTs; C+, secure generalizations from RCTs; C, observational evidence.

NOTE: Although some prophylactic anticoagulation therapies have not been evaluated in clinical trials for 4 weeks, we feel that all hip fracture patients should receive prophylaxis against venous thromboembolism for this duration, regardless of the drug used.

Another cost-effectiveness analysis of fondaparinux vs enoxaparin to prevent VTE in patients undergoing hip replacement, knee replacement, or hip fracture surgery in the United Kingdom[28] suggested that fondaparinux would lead to lower expected costs per patient and to fewer VTE-related events and deaths. However, these calculations were based on the pricing of fondaparinux and enoxaparin in the United Kingdom, which may not mirror US pricing; the rates of late DVT may also vary. It is also important to note that in US institutions, especially in acute care settings where discounts are routinely provided by the drug company, the lower discounted price of 40 mg once daily of enoxaparin would likely not lead to cost savings in favor of fondaparinux.

TAKE-HOME POINTS

Prompt and sufficient prophylaxis. Patients who develop VTE after hip fracture have significantly higher morbidity rates, longer hospital stays, and costs of inpatient care almost twice as high as those for patients with hip fracture who do not develop VTE.[29] Therefore, promptly starting and then continuing VTE prophylaxis for the optimal duration is very important.

Fondaparinux. The evidence to date seems to indicate that fondaparinux is the most effective agent. However, we believe the superiority in efficacy found in PENTHIFRA could have been due to the early dosing of fondaparinux and to the relatively late dosing of enoxaparin, ie, at 12 to 24 hours after surgery. Additionally, there are limitations to using fondaparinux perioperatively: it is contraindicated in patients who weigh less than 50 kg (110 lb) and in patients with a creatinine clearance rate below 30 mL/min. Therefore, it is important to estimate the patient's creatinine clearance rate before giving fondaparinux, since it is affected by both age and body mass.

Warfarin caveats. Despite limited evidence, warfarin is approved by the US Food and Drug Administration (FDA) for VTE prophylaxis in hip fracture patients. Although it is effective, history has shown it to be unpredictable, with many drug interactions. It also requires close and constant monitoring via frequent blood draws. Additionally, its long half-life prevents a therapeutic INR for at least 4 to 5 days after it is started. If warfarin is used, we recommend starting it immediately after surgery and aiming for an INR of 2.0 to 3.0 for 4 weeks.

We also suggest using a low-molecular-weight heparin or fondaparinux along with warfarin until the target INR is reached, given the increased risk of proximal VTE with warfarin vs enoxaparin.[30]

Heparins. Low-molecular-weight heparins such as enoxaparin and dalteparin have gained popularity recently compared with low-dose unfractionated heparin since they are well absorbed from subcutaneous tissue, are less likely to induce thrombocytopenia, and can be dosed once daily. The ability to give low-mol-

ecular-weight heparin preoperatively and the fact that it has few contraindications has led to its widespread acceptance despite the lack of FDA approval for hip fracture patients. The dose of enoxaparin can now also be adjusted in patients with creatinine clearance rates below 30 mL/min by decreasing the dose from 40 mg to 30 mg once daily.

Enoxaparin. Although the current evidence favors fondaparinux in efficacy, using enoxaparin 40 mg up to 12 hours preoperatively and resuming therapy 12 to 24 hours postoperatively is another strategy endorsed by the ACCP. Therapy should continue for 4 weeks.

TABLE 1 outlines the dosing regimens, duration of treatment, and recommendations from the ACCP for the commonly used prophylactic agents.

REFERENCES

1. **Popovic JR.** 1999 National Hospital Discharge Survey: annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 2001; 151:i–v, 1–206.
2. **Cummings SR, Rubin SM, Black D.** The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. Clin Orthop Relat Res 1990; 252:163–166.
3. **Wolinsky FD, Fitzgerald JF, Stump TE.** The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. Am J Public Health 1997; 87:398–403.
4. **Zuckerman JD.** Hip fracture. N Engl J Med 1996; 334:1519–1525.
5. **Frostick SP.** Death after joint replacement. Haemostasis 2000; 30 (suppl 2):84–87; discussion 82–83.
6. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl 3):338S–400S.
7. **Agnelli G, Cosmi B, Di Filippo P, et al.** A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. Thromb Haemost 1992; 67:203–208.
8. **Lowe GD, Campbell AF, Meek DR, Forbes CD, Prentice CR.** Subcutaneous ancrod in prevention of deep-vein thrombosis after operation for fractured neck of femur. Lancet 1978; 2:698–700.
9. **Powers PJ, Gent M, Jay RM, et al.** A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989; 149:771–774.
10. **Rogers PH, Walsh PN, Marder VJ, et al.** Controlled trial of low-dose heparin and sulfinpyrazone to prevent venous thromboembolism after operation on the hip. J Bone Joint Surg Am 1978; 60:758–762.
11. **Snook GA, Chrisman OD, Wilson TC.** Thromboembolism after surgical treatment of hip fractures. Clin Orthop Relat Res 1981; 155:21–24.
12. **Todd CJ, Freeman CJ, Camilleri-Ferrante C, et al.** Differences in mortality after fracture of hip: the east Anglian audit. BMJ 1995; 310:904–908.
13. **Eastwood EA, Magaziner J, Wang J, et al.** Patients with hip fracture: subgroups and their outcomes. J Am Geriatr Soc 2002; 50:1240–1249.
14. **Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM; the ESCORTE group.** Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. J Thromb Haemost 2005; 3:2006–2014.
15. **Hefley FG Jr, Nelson CL, Puskarich-May CL.** Effect of delayed admission to the hospital on the preoperative prevalence of deep-vein thrombosis associated with fractures about the hip. J Bone Joint Surg Am 1996; 78:581–583.
16. **Zahn HR, Skinner JA, Porteous MJ.** The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. Injury 1999; 30:605–607.
17. **Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ.** Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. J Orthop Trauma 1995; 9:1–7.
18. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295–1302.
19. **Borgstroem S, Greitz T, van der Linden W, Molin J, Rudics I.** Anticoagulant prophylaxis of venous thrombosis in patients with fractured neck of the femur; a controlled clinical trial using venous phlebography. Acta Chir Scand 1965; 129:500–508.
20. **Hamilton HW, Crawford JS, Gardiner JH, Wiley AM.** Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. J Bone Joint Surg Br 1970; 52:268–289.
21. **Monreal M, Lafoz E, Navarro A, et al.** A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. J Trauma 1989; 29:873–875.
22. **Jorgensen PS, Knudsen JB, Broeng L, et al.** The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. Clin Orthop Relat Res 1992; 278:95–100.
23. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. Haemostasis 1999; 29:310–317.
24. **Eriksson BI, Bauer KA, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345:1298–1304.
25. **Horlocker TT, Wedel DJ, Benzon H, et al.** Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003; 28:172–197.
26. **Eriksson BI, Lassen MR; PENTasaccharide in HIp-FRActure Surgery Plus Investigators.** Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003; 163:1337–1342.
27. **Wade WE, Spruill WJ, Leslie RB.** Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in hip fracture surgery. Am J Ther 2004; 11:194–198.
28. **Gordois A, Posnett J, Borris L, et al.** The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. J Thromb Haemost 2003; 1:2167–2174.
29. **Ollendorf DA, Vera-Llonch M, Oster G.** Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients. Am J Health Syst Pharm 2002; 59:1750–1754.
30. **Brotman DJ, Jaffer AK, Hurbanek JG, Morra N.** Warfarin prophylaxis and venous thromboembolism in the first 5 days following hip and knee arthroplasty. Thromb Haemost 2004; 92:1012–1017.

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