

New Oral Anticoagulants and Outpatient Prophylaxis of Venous Thromboembolism

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Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE),¹ is a serious complication after total hip arthroplasty (THA) and total knee arthroplasty (TKA).² In patients undergoing THA or TKA, the formation of blood clots usually starts in the deep vein of the calf,³ and leg scanning and venographic studies have shown that such thrombi often begin during surgery.³ Approximately one-half of such calf DVTs resolve spontaneously within 72 hours, although one-sixth to one-third may extend to involve the proximal veins.^{3,4} Although venous thrombi often begin perioperatively, studies have shown that the cumulative risk of VTE may last for up to 3 months after THA and 1 month after TKA.⁵ In addition, the timing of peak incidence of postoperative VTE differs with the type of surgery. Recent data from the Global Orthopaedic Registry (GLORY), a multinational group of 100 centers, suggest that in patients undergoing THA symptomatic VTE occurs approximately 10 days later than in patients undergoing TKA, with a mean time to VTE of 9.7 days for TKA and 21.5 days for THA.⁶

In the past, anticoagulation was given only during the hospital stay, normally 7 to 10 days, and was discontinued on discharge.⁷ However, hospital stays are becoming increasingly shorter. Data from GLORY showed that the median length of hospital stay is 4 days (range, 3-9 days) in patients with TKA and 5 days (range, 3-11 days) in patients with THA.⁶ Not all orthopedic surgeons are aware that more than half of symptomatic VTEs occur post-discharge (e.g., 75% of patients undergoing THA and 57% of patients undergoing TKA develop VTE after the median time to hospital discharge).⁶ In addition, a marked decrease in the use of thromboprophylaxis is seen at the time of discharge,⁶ although the burden of DVT following hospital discharge after THA or TKA is substantial.^{8,9} A meta-analysis of studies in which patients received only short-duration (7-10 days) anticoagulation after THA/TKA found that symptomatic, non-fatal VTE occurred in about 1 in 32 patients and fatal PE in about 1 in 1000 patients within 3 months of surgery.¹⁰ One study found that 10% of patients admitted with a VTE event were discharged without any anticoagulation. Of those, 36% had a malignancy and 26% had had a previous VTE event, both potentiating factors for further

Abstract

In total hip or total knee arthroplasty, hypercoagulability typically begins on the operating table and a hypercoagulable state persists for up to 3 months after surgery. For that reason, it is critical to begin anticoagulation as soon as possible after wound closure and to continue it beyond the standard time of hospital discharge: current guidelines recommend up to 35 days following total hip arthroplasty and at least 10 days following total knee arthroplasty. Currently, low molecular weight heparin is commonly used for in-hospital prophylaxis, while for post-discharge use, warfarin is the drug most frequently prescribed in the United States. While both are efficacious, both have challenges associated with administration and, in the case of warfarin, a narrow therapeutic window, both food and drug interactions, routine blood monitoring, and an unpredictable dose response. New oral anticoagulants are being developed that will be easier to administer, have minimal or no drug interactions, and do not require coagulation monitoring. These drugs, which include dabigatran, apixaban, and rivaroxaban, should encourage improved compliance with guideline recommendations for optimal duration of thromboprophylaxis and lead to a reduced incidence of venous thrombotic events.

(*Am J Manag Care.* 2011;17:S15-S21)

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Reports

VTE.¹¹ Another study found that only 19% of patients older than 65 years received post-discharge thromboprophylaxis after major hip or knee surgery.¹²

While continuing thromboprophylaxis as an outpatient may be warranted to prevent late-occurring VTE events,¹³ findings from the Hip and Knee Registry indicated that only two-thirds of patients are given adequate prophylaxis after discharge.¹⁴

Optimal Duration of Prophylaxis After Total Hip and Total Knee Arthroplasty

In patients undergoing joint arthroplasty in the lower limb, the 8th American College of Chest Physicians (ACCP) guidelines recommend at least 10 days of thromboprophylaxis. In patients with THA, ACCP guidelines recommend that thromboprophylaxis be extended up to 35 days, and for the first time, they suggest that in patients with TKA, prophylaxis may also be extended for 35 days, although the evidence is less strong in this group.² The fact that activation of coagulation and venous stasis are present for 5 to 6 weeks,¹⁵⁻¹⁷ along with the prolonged risk of VTE after THA, supports the guideline recommendation of extended thromboprophylaxis. A meta-analysis of data from randomized trials found that extended-duration prophylaxis after THA or TKA significantly reduced the frequency of post-discharge symptomatic VTE compared with placebo or untreated controls.¹⁸ However, the absolute reduction of symptomatic VTE in some studies and meta-analyses may have been overestimated by using venographic DVT to anticipate clinical events.¹⁹ Nevertheless, readmission rates for VTE during the 6 months after THA and TKA were found to be reduced by extended (6 weeks) warfarin administration compared with no outpatient prophylaxis.^{20,21}

What Prophylaxis Do Patients Currently Receive?

After THA or TKA, the ACCP guidelines recommend thromboprophylaxis with a low molecular weight heparin (LMWH), fondaparinux, or an adjusted-dose vitamin K antagonist, usually warfarin. The guidelines specifically recommend against using acetylsalicylic acid (ASA) alone.² The American Association of Orthopaedic Surgeons (AAOS) guidelines for the prevention of PE recommend the same anticoagulants but also include ASA.²² The AAOS panelists rejected DVT as an outcome because they considered that the link between DVT and PE after THA or TKA was unproven. However, their argument excluded data from important and relevant clinical trials, and they used Level 3 data for support.²³ The AAOS also recommends using ASA

for patients at high risk of PE and/or major bleeding.²² This recommendation is largely based on expert opinion, however, and lacks a strong scientific basis.²³

Although almost all patients undergoing TKA and THA receive some form of prophylaxis for VTE, there appears to be considerable variation in the routine practice of orthopedic surgeons. A large proportion of patients do not receive the ACCP guideline-recommended prophylaxis for VTE in terms of type of prophylaxis, start time, and duration of thromboprophylaxis. GLORY investigators assessed the compliance of clinicians from the United States and 12 other countries with the 6th ACCP guidelines (which were released in 2001).^{24,25} Warfarin was used more frequently in the United States, while LMWH was used more frequently in other countries.²⁵ Approximately one-third of patients who received LMWH did not receive it at the guideline-recommended starting time, nor for the appropriate duration.²⁵ Less than one-half of patients with TKA and less than one-third of patients with THA were fully compliant with warfarin use.²⁵ The inadequate use of thromboprophylaxis leaves a significant proportion of patients at risk of developing venous thromboembolic events at a later time.²⁶ While extended thromboprophylaxis with LMWHs^{27,28} (specifically enoxaparin²⁹ and dalteparin^{30,31}) and fondaparinux³² was found to be effective after THA, data to support extended prophylaxis after TKA are less robust.^{13,29}

Drawbacks of Currently Available Agents for Thromboprophylaxis

LMWHs are the current standard of care for thromboprophylaxis after THA and TKA in many countries, including those in the European Union and Canada.³³ The LMWHs are efficacious, have acceptable bleeding risks, and do not need routine coagulation monitoring.³⁴ However, they are perceived to be more costly compared with warfarin, and need to be administered subcutaneously, making their use as post-discharge prophylaxis problematic, as patients who cannot or are unwilling to self-inject may need to attend daily appointments or receive daily nurse visits to administer their medication. There must also be appropriate and safe disposal facilities for syringes and needles. Nevertheless, LMWHs are safe and effective as outpatient-based therapy.³⁵ Drawbacks of the LMWHs include a very low potential risk of heparin-induced thrombocytopenia.³⁶ In addition, the current in-hospital length of stay is inadequate for patients who are to be “bridged” from LMWH to warfarin for outpatient thromboprophylaxis, as guidelines recommend concomitant use of both agents for 4 to 5 days and until the

international normalized ratio (INR) is in the target range for 2 days.³⁷ This may result in inadequate post-discharge thromboprophylaxis.

Warfarin is one of the most frequently used pharmacologic thromboprophylaxis agents in the United States, along with the LMWHs.²⁵ While it is efficacious, warfarin has a narrow therapeutic window. Moreover, due to its pharmacokinetics and pharmacodynamics, there is considerable intra- and interpatient variability in the dose response.³⁷ Polymorphisms in the genes encoding for the cytochrome P450 2C9 enzyme, and the vitamin K epoxide reductase, have been shown to contribute to variability in sensitivity to warfarin.³⁸ Warfarin is also associated with multiple drug-drug and food-drug interactions.³⁷ Regular coagulation monitoring is required to maintain the INR within the narrow optimal therapeutic range of 2 to 3.^{2,39} In fact, many patients' laboratory values are not within the required therapeutic range^{40,41} for significant periods during prophylaxis, although 1 study reported that 92% of patients had an INR greater than 1.7 at the time of hospital discharge.⁴²

The use of fondaparinux after major orthopedic surgery remains limited. Clinical trials have evaluated fondaparinux only up to day 11 after THA and TKA.⁴³ The drawbacks of fondaparinux include its subcutaneous mode of administration, its relatively long half-life, and its perceived association with increased bleeding. In addition, caution is recommended when it is used in the elderly and in patients weighing less than 50 kg, due to an increased risk of bleeding.⁴⁴

Reversal of anticoagulation is fortunately infrequently required in short-term use, as reversal is not easy. Protamine is only partially effective with the LMWHs⁴⁵ and ineffective with fondaparinux.⁴⁴ Warfarin reversal can be achieved by administration of vitamin K, and for serious bleeding, by the use of fresh frozen plasma, prothrombin complex concentrates, or recombinant activated Factor VII.⁴⁶ However, reversal can be slow and difficult. As a result, stopping anticoagulation, supportive therapy, and appropriate treatment, including surgery, are normally used for any emergency until spontaneous reversal is achieved, especially with agents with a short half-life, such as the newer anticoagulants. The use of other modalities, such as recombinant activated Factor VII and prothrombin complex concentrates, may be useful as adjuvants but are as yet relatively unproven.⁴⁷

Strategies to Improve Prophylaxis

As indicated by the GLORY registry,²⁵ physician compliance with guidelines appears to be poor. Management of prophylaxis should obviously begin in the hospital.

The guidelines recommend that every hospital have a formal, active strategy that addresses the prevention of VTE. Guidelines also call for a local thromboprophylaxis strategy in the form of a written, institutionwide thromboprophylaxis policy.² (See also the article by Merli in this supplement.⁴⁸) Strategies shown to increase thromboprophylaxis adherence, including computer-based decision support systems, preprinted orders, and periodic audit and feedback, are also recommended, while passive methods are not.² Computer-based decision support systems and reminders have been shown to change physician behavior and increase the use of prophylaxis.⁴⁹⁻⁵¹ A further step might be to simplify the prescription process.⁵² In addition, the previous ACCP guidelines suggest that resources be devoted to patient-mediated interventions.⁵³ Multiple strategies are more likely to improve practice.

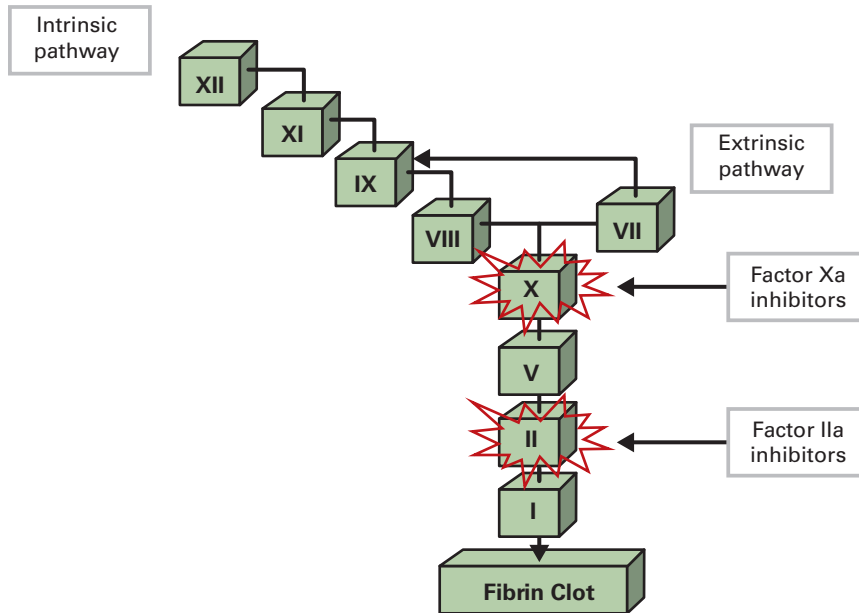
While strategies have been developed for patient education about anticoagulation with warfarin,⁵⁴ similar strategies will need to be developed for patient education about anticoagulation with the new oral agents (see below). Poor patient adherence to medication has been well documented,⁵⁵ and this has also been evident with anticoagulation therapy.⁵⁶ There are many reasons for poor adherence, but the drawbacks listed above for the established therapies probably contribute.⁵⁷ After appropriate patient education, adherence to new oral anticoagulant treatments should be at least as good as that for the established anticoagulants.⁵⁸ Therefore, the advent of new orally active anticoagulants should result in an improvement in the prevention of VTE.⁵⁹ In addition, the adoption of new courses on anticoagulation therapy for pharmacy students should also increase the understanding of issues associated with anticoagulation.⁶⁰

Novel Anticoagulants

Several new anticoagulants are in clinical development, with the aim of providing safe, effective, and more convenient alternatives to the currently available agents for the prevention of VTE after THA and TKA. Unlike the current agents, these new anticoagulants have selective targets in the coagulation cascade (**Figure**).^{61,62}

Apixaban is an oral, direct Factor Xa inhibitor in phase III clinical trials for the prevention and treatment of thromboembolic disorders. A brief overview of the ADVANCE-1 (Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 1)⁶³ and ADVANCE-2 (Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 2)⁶⁴ studies is given in the

■ **Figure.** Coagulation Cascade and Factor Xa and Factor IIa as Targets⁶¹



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article by Merli in this supplement.⁴⁸ Rivaroxaban, another oral, direct Factor Xa inhibitor, has been approved in more than 95 countries for the prevention of VTE after elective THA and TKA. Results of the RECORD (REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) program showed that rivaroxaban 10 mg once daily significantly reduced the incidence of the composite of symptomatic VTE and all-cause mortality compared with enoxaparin regimens of 40 mg once daily, and total VTE when compared with 30 mg enoxaparin twice daily.⁶⁵⁻⁶⁸ A thorough overview of the RECORD program is given in the article by Kwong in this supplement.⁶⁹

Dabigatran etexilate is an oral, direct thrombin inhibitor that is approved in the European Union and Canada for the prevention of VTE after THA and TKA. RE-NOVATE (Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip arthroplasty) was a double-blind trial in which patients with THA were randomized to dabigatran 220 mg or 150 mg or enoxaparin 40 mg per day for a median of 33 days. The primary efficacy outcome, a composite of venographic or symptomatic VTE and death from all causes, occurred in 6.0% of patients receiving dabigatran 220 mg, 8.6% of those receiving dabigatran 150 mg, and 6.7% of patients receiving enoxaparin, with no significant

difference in major bleeding with either dose of dabigatran compared with enoxaparin. However, in 2 trials conducted in patients undergoing TKA, dabigatran met the non-inferiority criteria vs enoxaparin 40 mg sc once daily in reducing total VTE and all-cause mortality in 1, RE-MODEL (Oral dabigatran etexilate versus subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee arthroplasty), but failed to do so vs 30 mg enoxaparin twice daily in the other, RE-MOBILIZE (Oral thrombin inhibitor dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total knee arthroplasty).⁷⁰⁻⁷²

The characteristics of these new agents are given in the

Table.^{73,74} All of them have the potential to improve adherence to guidelines for extended thromboprophylaxis.⁷⁵

Conclusions

Although the high risk of VTE in patients after THA and TKA is well recognized, understanding the timing of clot formation is essential for the optimal prevention and management of these events. Because they are needed to achieve hemostasis, hypercoagulability and clots may start on the operating table. This suggests that anticoagulation needs to be started in the perioperative period. Most early DVTs after major orthopedic surgery begin in the calf and approximately half of them resolve spontaneously. Thrombi that remain confined to the calf rarely become symptomatic, and some surgeons may doubt the need to actively manage asymptomatic events. However, there is evidence that, in the absence of treatment, approximately one-sixth to one-third of isolated distal DVTs extend to involve the proximal veins, which makes them more likely to be symptomatic and to increase the risk of PE.

Taking into consideration how early clots form after THA and TKA and how long clot formation may continue, both initiation and duration of prophylaxis are suboptimal in current prophylactic practice. As more than half of symptomatic events occur after hospital discharge, continuing thromboprophylaxis post-discharge is vital in preventing late-occurring

■ **Table.** Comparison of Apixaban, Rivaroxaban, and Dabigatran^{73,74}

	Apixaban	Rivaroxaban	Dabigatran
Route of administration	Oral	Oral	Oral
Target	Factor Xa	Factor Xa	Thrombin (Factor IIa)
Dosing	Twice daily	Once daily	Twice daily
Monitoring required	No	No	No
Drug-drug interactions	P-glycoprotein inhibitors and CYP3A4 inhibitors	P-glycoprotein inhibitors and CYP3A4 inhibitors	P-glycoprotein inducers
Bioavailability	43%-46%	60%-80%	3%-7%
Half-life (hours)	8-15	7-11	12-17
Mode of elimination	Fecal (56%), renal (25%)	Two-thirds metabolized, half renal and half fecal, final third direct renal excretion as unchanged compound	

CYP3A4 indicates cytochrome P450 3A4.

VTE. This is particularly important in patients undergoing THA, due to the prolonged risk documented in this patient population. Current anticoagulants have characteristics that make them challenging for post-discharge thromboprophylaxis and that may contribute to the observed poor adherence with clinical guidelines. New anticoagulants in development are oral, can be given in a fixed dose, have been found to have a good pharmacokinetic and pharmacodynamic profile, have minimal drug-drug or drug-food interactions, and do not require coagulation monitoring—all features that will make them easier to use in the outpatient setting after THA or TKA.

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Funding Source: Financial support for this supplement was provided by Ortho-McNeil Janssen Scientific Affairs, LLC and Johnson & Johnson Worldwide Market Access.

Author Disclosure: Dr Fisher received grants/honoraria from Bayer, Portola, sanofi-aventis, and Takeda. He has received lectureship fees from Bayer, Boehringer Ingelheim, Johnson & Johnson, and sanofi-aventis.

Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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REFERENCES

1. **McRae SJ, Ginsberg JS.** Initial treatment of venous thromboembolism. *Circulation.* 2004;110:13-19.
2. **Geerts WH, Bergqvist D, Pineo GF, et al.** Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest.* 2008;133:381S-453S.
3. **Kearon C.** Natural history of venous thromboembolism. *Circulation.* 2003;107:122-130.
4. **Kakkar VV, Howe CT, Flanc C, Clarke MB.** Natural history of postoperative deep-vein thrombosis. *Lancet.* 1969;2:230-232.
5. **Bjornara BT, Gudmundsen TE, Dahl OE.** Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br.* 2006;88:386-391.
6. **Warwick D, Friedman RJ, Agnelli G, et al.** Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. *J Bone Joint Surg Br.* 2007;89:799-807.
7. **Fisher WD, Turpie AG.** Outpatient thromboprophylaxis after hip or knee surgery: discrepancies and concerns. *CMAJ.* 2008;178:1571-1572.
8. **Nutescu EA, Shorr AF, Farrelly E, Horblyuk R, Happe LE, Franklin M.** Burden of deep vein thrombosis in the outpatient setting following major orthopedic surgery. *Ann Pharmacother.* 2008;42:1216-1221.
9. **Arcelus JI, Kudrna JC, Caprini JA.** Venous thromboembolism following major orthopedic surgery: what is the risk after discharge? *Orthopedics.* 2006;29:506-516.
10. **Douketis JD, Eikelboom JW, Quinlan DJ, Willan AR, Crowther MA.** Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Intern Med.* 2002;162:1465-1471.
11. **Caprini JA, Tapson VF, Hyers TM, et al.** Treatment of venous thromboembolism: adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. *J Vasc Surg.* 2005;42:726-733.
12. **Rahme E, Dasgupta K, Burman M, et al.** Postdischarge thromboprophylaxis and mortality risk after hip- or knee-replacement surgery. *CMAJ.* 2008;178:1545-1554.
13. **Friedman RJ.** Optimal duration of prophylaxis for venous thromboembolism following total hip arthroplasty and total knee arthroplasty. *J Am Acad Orthop Surg.* 2007;15:148-155.
14. **Anderson FA Jr, Hirsh J, White K, Fitzgerald RH Jr.** Temporal trends in prevention of venous thromboembolism following primary total hip or knee arthroplasty 1996-2001: findings from the Hip and Knee Registry. *Chest.* 2003;124:349S-356S.

15. Dahl OE, Aspelin T, Arnesen H, et al. Increased activation of coagulation and formation of late deep venous thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thromb Res*. 1995;80:299-306.
16. McNally MA. The influence of total knee replacement on lower limb blood flow. *J R Coll Surg Edinb*. 1997;42:286-287.
17. McNally MA, Mollan RA. Total hip replacement, lower limb blood flow and venous thrombogenesis. *J Bone Joint Surg Br*. 1993;75:640-644.
18. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001;358:9-15.
19. O'Donnell M, Linkins LA, Kearon C, Julian J, Hirsh J. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med*. 2003;163:1362-1366.
20. Pellegrini VD Jr, Donaldson CT, Farber DC, Lehman EB, Evarts CM. The John Charnley Award: prevention of readmission for venous thromboembolic disease after total hip arthroplasty. *Clin Orthop Relat Res*. 2005;441:56-62.
21. Pellegrini VD Jr, Donaldson CT, Farber DC, Lehman EB, Evarts CM. The Mark Coventry Award: prevention of readmission for venous thromboembolism after total knee arthroplasty. *Clin Orthop Relat Res*. 2006;452:21-27.
22. Johanson NA, Lachiewicz PF, Lieberman JR, et al. Prevention of symptomatic pulmonary embolism in patients undergoing total hip and knee arthroplasty. *J Am Acad Orthop Surg*. 2009;17:183-196.
23. Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: what are the implications for clinicians and patients? *Chest*. 2009;135:513-520.
24. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest*. 2001;119:132S-175S.
25. Friedman RJ, Gallus AS, Cushner FD, Fitzgerald G, Anderson FA Jr. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. *Curr Med Res Opin*. 2008;24:87-97.
26. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med*. 1998;158:1525-1531.
27. Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty--a meta-analysis. *Thromb Haemost*. 2001;85:940-941.
28. Muntz J. Thromboprophylaxis in orthopedic surgery: how long is long enough? *Am J Orthop*. 2009;38:394-401.
29. Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *J Bone Joint Surg Am*. 2001;83-A:336-345.
30. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. *Arch Intern Med*. 2000;160:2208-2215.
31. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135:858-869.
32. Eriksson BI, Lassen MR. 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.
33. Prandoni P. Prevention and treatment of venous thromboembolism with low-molecular-weight heparins: clinical implications of the recent European guidelines. *Thromb J*. 2008;6:13.
34. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:188S-203S.
35. Spyropoulos AC. Outpatient-based primary and secondary thromboprophylaxis with low-molecular-weight heparin. *Clin Appl Thromb Hemost*. 2008;14:63-74.
36. Warkentin TE, Greinacher A, Koster A, Lincoff AM; American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest*. 2008;133:340S-380S.
37. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest*. 2008;133:160S-198S.
38. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med*. 2008;358:999-1008.
39. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost*. 2003;90:446-455.
40. Verhovsek M, Motlagh B, Crowther MA, et al. Quality of anticoagulation and use of warfarin-interacting medications in long-term care: a chart review. *BMC Geriatr*. 2008;8:13.
41. Levi M. Self-management of anticoagulation. *Expert Rev Cardiovasc Ther*. 2008;6:979-985.
42. Anderson DR, Wilson SJ, Blundell J, et al. Comparison of a nomogram and physician-adjusted dosage of warfarin for prophylaxis against deep-vein thrombosis after arthroplasty. *J Bone Joint Surg Am*. 2002;84-A:1992-1997.
43. 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.
44. Arixtra (fondaparinux sodium 5 mg, 7.5 mg, 10 mg injection) summary of product characteristics. <http://emc.medicines.org.uk/medicine/15937>. Accessed November 1, 2010.
45. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119:64S-94S.
46. Hanley JP. Warfarin reversal. *J Clin Pathol*. 2004;57:1132-1139.
47. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood*. 2008;111:4871-4879.
48. Merli G. Quality improvement program: advancement of hospital venous thromboembolism-free zones. *Am J Manag Care*. 2011;17:S9-S14.
49. Durieux P, Nizard R, Ravaut P, Mounier N, Lepage E. A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. *JAMA*. 2000;283:2816-2821.
50. Mosen D, Elliott CG, Egger MJ, et al. The effect of a computerized reminder system on the prevention of postoperative venous thromboembolism. *Chest*. 2004;125:1635-1641.
51. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N Engl J Med* 2005;352:969-977.
52. Tooher R, Middleton P, Pham C, et al. A systematic review of strategies to improve prophylaxis for venous thromboembolism in hospitals. *Ann Surg*. 2005;241:397-415.
53. Schunemann HJ, Cook D, Grimshaw J, et al. Antithrombotic and thrombolytic therapy: from evidence to application: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:688S-696S.

- 54. Wofford JL, Wells MD, Singh S.** Best strategies for patient education about anticoagulation with warfarin: a systematic review. *BMC Health Serv Res.* 2008;8:40.
- 55. Osterberg L, Blaschke T.** Adherence to medication. *N Engl J Med.* 2005;353:487-497.
- 56. McBride D, Bruggenjurgan B, Roll S, Willich SN.** Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. *J Thromb Thrombolysis.* 2007;24:65-72.
- 57. Kneeland PP, Fang MC.** Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. *Patient Prefer Adherence.* 2010;4:51-60.
- 58. Bellamy L, Rosencher N, Eriksson B.** Adherence to a new oral anticoagulant treatment prescription: dabigatran etexilate. *Patient Prefer Adherence.* 2009;3:173-177.
- 59. Lassen MR, Laux V.** Emergence of new oral antithrombotics: a critical appraisal of their clinical potential. *Vasc Health Risk Manag.* 2008;4:1373-1386.
- 60. Hornsby LB.** An anticoagulation therapy elective for third-year pharmacy students. *Am J Pharm Educ.* 2009;73:119.
- 61. Ansell J.** Factor Xa or thrombin: is factor Xa a better target? *J Thromb Haemost.* 2007;5(suppl 1):60-64.
- 62. Weitz JI, Bates SM.** New anticoagulants. *J Thromb Haemost.* 2005;3:1843-1853.
- 63. 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.
- 64. Lassen MR, Raskob GE, Pineo GF, et al.** Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet.* 2010;375:807-815.
- 65. Eriksson BI, Borris LC, Friedman RJ, et al.** Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med.* 2008;358:2765-2775.
- 66. Kakkar AK, Brenner B, Dahl OE, et al.** Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet.* 2008;372:31-39.
- 67. Lassen MR, Ageno W, Borris LC, et al.** Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med.* 2008;358:2776-2786.
- 68. Turpie AGG, Lassen MR, Davidson BL, et al.** Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet.* 2009;373:1673-1680.
- 69. Kwong LM.** Cost-effectiveness of rivaroxaban after total hip or total knee arthroplasty. *Am J Manag Care.* 2011;17:S22-S26
- 70. Eriksson BI, Dahl OE, Rosencher N, et al.** Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;370:949-956.
- 71. Eriksson BI, Dahl OE, Rosencher N, et al.** Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost.* 2007;5:2178-2185.
- 72. Ginsberg JS, Davidson BL, Comp PC, et al.** Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty.* 2009;24:1-9.
- 73. Eriksson BI, Quinlan DJ, Weitz JI.** Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet.* 2009;48:1-22.
- 74. Pradaxa® (dabigatran etexilate mesylate) prescribing information.** Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, October 2010.
- 75. Borris LC.** Rivaroxaban and dabigatran etexilate: two new oral anticoagulants for extended postoperative prevention of venous thromboembolism after elective total hip arthroplasty. *Arch Orthop Trauma Surg.* 2009;129:1441-1445.