Therapeutic Class Overview
Injectable Anticoagulants

Therapeutic Class

- **Overview/Summary:** The injectable anticoagulants include low molecular weight heparin (LMWH) agents (dalteparin [Fragmin®], enoxaparin [Lovenox®]) and factor Xa inhibitors (fondaparinux [Arixtra®]). In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism. Certain agents within the class are also approved for the treatment of acute ST-segment elevation myocardial infarction or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The specific FDA-approved indications of the injectable anticoagulants are outlined in Table 1.[1-3] The LMWH agents exert their effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including factor Xa and thrombin. LMWH is a smaller fragment of unfractionated heparin (UFH) formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH (3,000 to 30,000 daltons) contributes to the chief difference between the agents. LMWH primarily inhibits factor Xa and has much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this to occur while the LMWH molecules typically are not.[4,5] Fondaparinux is a synthetic factor Xa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-factor Xa activity is higher than that of the LMWH agents. Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable.[5] Currently, enoxaparin and fondaparinux are available generically.[6,7]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dalteparin (Fragmin®)	Extended treatment of symptomatic venous thromboembolism (proximal deep vein thrombosis and/or pulmonary embolism) in patients with cancer*, prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications and in patients undergoing hip fracture surgery	Injection: 2,500 IU/0.2 mL‡ 5,000 IU/0.2 mL‡ 7,500 IU/0.3 mL‡ 10,000 IU/0.4 mL‡ 10,000 IU/1 mL§ 12,500 IU/0.5 mL‡ 15,000 IU/0.6 mL‡ 18,000 IU/0.72 mL‡ 95,000 IU/3.8 mL‖ 95,000 IU/9.5 mL‖	-
Enoxaparin (Lovenox®¶)	Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip replacement surgery#, in patients undergoing knee replacement	Injection (100 mg/mL): 30 mg/0.3 mL‡ 40 mg/0.4 mL‡ 60 mg/0.6 mL§ 80 mg/0.8 mL§ 100 mg/1 mL§ 300 mg/3 mL‡‡ Injection (150 mg/mL):	✔

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	surgery, treatment of acute deep vein thrombosis**, treatment of acute ST-segment elevation myocardial infarction††	120 mg/0.8 mL§ 150 mg/1 mL§	
Fondaparinux (Arixtra®¶)	Prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip fracture surgery§§, in patients undergoing hip replacement surgery, in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis‖‖, treatment of acute pulmonary embolism¶¶	Injection: 2.5 mg/0.5 mL‡ 5 mg/0.4 mL‡ 7.5 mg/0.6 mL‡ 10 mg/0.8 mL‡	✔

IU=international units
*In these patients therapy begins with the initial venous thromboembolism treatment and continues for six months.
†When concurrently administered with aspirin therapy.
‡Available as a single-dose prefilled syringe.
§Available as a single-dose graduated prefilled syringe.
‖Available as a multiple-dose vial. After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to two weeks.
¶Generic available in at least one dosage form and/or strength.
#During and following hospitalization.
**Indicated for inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin, and for outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction receiving thrombolysis and being managed medically or with percutaneous coronary intervention.
‡‡Available as a multi-dose vial.
§§Including extended prophylaxis.
‖‖When administered in conjunction with warfarin.
¶¶When administered in conjunction with warfarin when initial therapy is administered in the hospital.
***With or without pulmonary embolism when administered in conjunction with warfarin.

Evidence-based Medicine

- A Cochrane Review (16 randomized controlled trials) of cancer patients receiving initial treatment for venous thromboembolism (VTE), revealed that low molecular weight heparin (LMWH) agents may be "superior" to unfractionated heparin (UFH) due to an observed nonsignificant advantage of these agents for reducing the incidence of recurrent VTE. No difference between LMWH agents and fondaparinux was observed for this outcome, or for the incidence of major and minor bleeding events. No significant differences were observed between dalteparin and tinzaparin for the incidence of VTE or major bleeding. With regards to mortality, a significant difference between LMWH agents and UFH was observed, which favored LMWH agents.[8]
- Several placebo-controlled trials, meta-analyses, and systematic reviews evaluating the injectable anticoagulants in medical patients, immobilized patients, and in those undergoing an orthopedic surgery have been conducted and consistently demonstrate their safety and efficacy for VTE treatment and/or thromboprophylaxis.[9-22]
- When the injectable anticoagulants are compared to other methods of thromboprophylaxis (e.g., heparin, UFH, warfarin), "superiority", in terms of recurrent VTE and safety, is not always consistent.[23-41]
- Although data comparing the safety and efficacy of the LMWH agents to fondaparinux have not consistently demonstrated significant "superiority" of one therapy in all comparisons, treatment with fondaparinux appears to be associated with a lower incidence of VTE and a comparable incidence of major bleeding compared to enoxaparin.[42-45] However, in a meta-analysis, the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with fondaparinux

compared to LMWH therapy (enoxaparin).[46] Another trial demonstrated no difference between fondaparinux and dalteparin for the incidence of VTE and bleeding.[47]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - For total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment, a low molecular weight heparin (LMWH) is suggested in preference to other agents recommended as alternatives (fondaparinux, apixaban, dabigatran, rivaroxaban, low dose unfractionated heparin (UFH), vitamin K antagonist (VKA), or aspirin). Extended prophylaxis (up to 35 days) may be required in certain clinical situations.[48]
  - For the prevention of venous thromboembolism (VTE) in acutely ill medical patients, LMWH agents, UFH, and fondaparinux are recommended, while LMWH agents and VKAs are recommended in patients with cancer.[48]
  - For the treatment of an acute deep vein thrombosis (DVT) or pulmonary embolism (PE), initial anticoagulation with a LMWH agent or fondaparinux is recommended over UFH for at least five days (until the International Normalized Ratio is at least 2.0 or greater for 24 hours). A VKA should also be initiated on the first day of treatment and continued for a period of three months. Extended prophylaxis with a VKA may be required in certain clinical conditions.[48]
    - Because patients with cancer are at high risk, it is recommended that initial treatment of an acute DVT or PE with a LMWH agent continue for the first three to six months, followed by indefinite therapy with either a VKA or LMWH agent.
  - Injectable anticoagulants are recommended in the management of non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarctions. Use of a specific agent over another is based on individual patient risk factors, as well as the timing and intensity of other planned management strategies.[49-51]
- Other Key Facts:
  - Enoxaparin and fondaparinux are available generically.

References

1. Fragmin® [package insert]. New York (NY): Pfizer Inc; 2010 Oct.
2. Lovenox® [package insert]. Greenville (NC): Sanofi-aventis U.S. LLC; 2013 Jun.
3. Arixtra® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2012 Jan.
4. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98.
5. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:141S-59S.
6. FDA approves first generic enoxaparin sodium injection [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2010 Jul 23 [cited 2013 Jul 2]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm.
7. FDA OKs Dr. Reddy's generic version of Arixtra [article on the internet]. New York City (NY): Bloomberg L.P.; 2011 Jul 13 [cited 2013 Jul 2]. Available from: http://www.businessweek.com/ap/financialnews/D9OET16G0.htm.
8. Akl EA, Vasireddi SR, Gunukula S, Barba M, Sperati F, Terrenato I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database of Systematic Reviews. 2011, Issue 2. Art. No.:CD006649. DOI:10.1002/14651858.CD006649.pub3.
9. Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low-molecular weight heparin. Arthroscopy. 2002;18(3):257-63.
10. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejo Bro JP, Anderson G, et al. Efficacy and safety of prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) after total hip arthroplasty-The Danish Prolonged Prophylaxis (DaPP) Study. Throm Res. 1998;89:281-7.
11. Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-9.
12. Torholm C, Broeng L, Seest Jorgensen P, Bjerregaard P, Josephsen L, Korsholm Jorgensen P, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. J Bone Joint Surg (Br). 1991;73-B:434-8.
13. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975-80.
14. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Nicol P, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility. Ann Intern Med. 2010;153:8-18.

15. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793-800.
16. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. Blood Coagul Fibrinolysis. 2003;14:341-6.
17. Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al. Low-molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.
18. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomized comparison of enoxaparin vs placebo. Lancet. 1996;348:224-8.
19. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci. 2008;13:442-51.
20. 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;163:1337-42.
21. Testroote M, Stigter WAH, de Visser DC, Janzing HMJ. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database of Systematic Reviews. 2008, Issue 4. Art. No.:CD006681. DOI:10.1002/14651858.CD006681.pub2.
22. Brookenthal KR, Freedman KB, Lotke PA, Fitzgerald RH, Lonner JH. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. J Arthroplasty. 2001;16(3):293-300.
23. Francis CW, Pellegrini VD, Totterman S, Boyd AD, Marder VJ, Liebert KM, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am. 1997;79:1365-72.
24. Eriksson BI, Kalebo P, Anthymyr BA, Wadenvik H, Tengborn L, Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. J Bone Joint Surg Am. 1991;73:484-93.
25. Colwell CW, Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am. 1999;81:932-40.
26. Fitzgerald RH, Spiro TE, Trowbridge AA, Gardiner GA, Whitsett TL, O'Connell MB, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am. 2001;83:900-6.
27. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, l'Esperance B, Demers C, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med. 1996;124:619-26.
28. No authors listed. Low-molecular-weight heparin (enoxaparin) vs dextran 70. The prevention of postoperative deep vein thrombosis after total hip replacement. Arch Intern Med. 1991;151:1621-4.
29. Senaran H, Acaroglu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophlyaxis in total hip replacement patients. Arch Orthop Trauma Surg. 2006;126:1-5.
30. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin vs low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Ann Surg. 2001;233(3):438-44.
31. Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Floshbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J. 2003;145:614-21.
32. De A, Roy P, Garg VK, Pandey NK. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. Blood Coagul Fibrinolysis. 2010;21:57-61.
33. Colwell CW, Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Balham JD, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 1994;76:3-14.
34. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin vs usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119:1062-72.
35. van der Heijden JF, Hutten BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term management of symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2001, Issue 3. Art. No.:CD002001. DOI:10.1002/14651858.CD002001.
36. Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors vs vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. Cochrane Database of Systematic Reviews. 2010, Issue 4. Art. No.:CD005981. DOI:10.1002/14651858.CD005981.pub2.
37. Erkens PMG, Prins MH. Fixed dose subcutaneous low molecular weight heparins vs adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database of Systematic Reviews. 2010, Issue 9. Art. No.:CD001100. DOI:10.1002/14651858.CD001100.pub3.
38. Othieno R, Abu Affan M, Okpo E. Home vs in-patient treatment for deep vein thrombosis. Cochrane Database of Systematic Reviews. 2007, Issue 3. Art. No.:CD003076. DOI:10.10002/14651858.CD003076.pub2.
39. Kanaan AO, Silva MA, Donovan JL, Roy T, Al-Homsi AS. Meta-analysis of venous thromboembolism prophylaxis in medically ill patients. Clin Ther. 2007;29(11):2395-405.
40. Handoll HHG, Farrar MJ, McBirnie J, Tytherleigh-Strong GM, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database of Systematic Reviews. 2002, Issue 4. Art. No.:CD000305. DOI:10.1002/14651858.CD000305.
41. Rasmussen MS, Jorgensen LN, Willie-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database of Systematic Reviews. 2009, Issue 1. Art. No.: CD004318. DOI:10.1002/14651858.CD004318.pub.

42. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux vs preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715-20.
43. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-10.
44. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-304.
45. Turpie AFF, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux vs postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet. 2002;359:1721-6.
46. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. Arch Intern Med. 2002;162:1833-40.
47. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux vs perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212-20.
48. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(Suppl 2):7-47.
49. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jun 11;61(23):e179-347.
50. Hamm CW, Bassand JP, Agewell S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology. Eur Heart J. 2011 Dec;32(23):2999-3054.
51. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29;61(4):485-510.

Therapeutic Class Review
Injectable Anticoagulants

Overview/Summary

The injectable anticoagulants include dalteparin (Fragmin®), enoxaparin (Lovenox®), and fondaparinux (Arixtra®). Dalteparin and enoxaparin are classified as low molecular weight heparins (LMWH), and fondaparinux is a selective factor Xa inhibitor. In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The specific FDA-approved indications for the injectable anticoagulants are outlined in Table 2.[1-3]

The LMWH agents exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including factor Xa and thrombin. A LMWH is a smaller fragment of unfractionated heparin (UFH) that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH (3,000 to 30,000 daltons) contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit factor Xa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this to occur while the LMWH molecules typically are not.[4,5] Fondaparinux is a synthetic factor Xa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-factor Xa activity is higher than that of the LMWH agents.[5] Currently, enoxaparin and fondaparinux are the only injectable anticoagulants that are available generically.[6,7] Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable.[5]

Clinical guidelines support the use of the injectable anticoagulants in FDA-approved indications.[8-15] According to the American College of Chest Physicians (ACCP) 9th edition 2012 evidence-based guidelines, LMWH, fondaparinux, apixaban (Eliquis®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), low dose UFH, adjust-dose vitamin K antagonist (VKA) therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients undergoing total hip or knee arthroplasty. Use of LMWH, fondaparinux, low dose UFH, adjusted-dose VKA therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients receiving hip fracture surgery. In these orthopedic surgeries thromboprophylaxis is recommended for a minimum of 10 to 14 days; however, for major orthopedic surgeries it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of the surgery. In addition, for total hip or knee arthroplasty and hip fracture surgery, thromboprophylaxis with LMWH is suggested in preference to the other recommended agents. For patients who decline or who are uncooperative with injections or intermittent pneumatic compression devices, apixaban or dabigatran is recommended over alternative forms of thromboprophylaxis, with rivaroxaban or adjusted-dose VKA therapy recommended if these two therapies are unavailable. Non-orthopedic surgical patients (e.g., general and abdominal-pelvic surgery) at moderate to high risk for VTE, who are not at high risk for bleeding complications, should receive thromboprophylaxis with LMWH or low dose UFH, and extended (four weeks) LMWH is recommended in high risk non-orthopedic surgical patients with cancer who are not otherwise at high risk for major bleeding complications. For prevention of VTE in nonsurgical patients (i.e., medical patients), thromboprophylaxis with LMWH, low dose UFH, or fondaparinux is recommended in acutely ill hospitalized patients at increased risk of thrombosis. Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding, thromboprophylaxis with LMWH or low dose UFH is suggested. The ACCP recommends parenteral anticoagulation (LMWH, fondaparinux, or UFH) for a minimum of five days for the treatment of acute deep vein thrombosis or pulmonary embolism, with the addition of early initiation of VKA therapy. With regards to parenteral anticoagulation for acute deep vein thrombosis or pulmonary embolism treatment, LMWH or

fondaparinux is suggested over UFH. Duration of anticoagulation after treatment of an acute event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor, and if it was the first or second thromboembolic event.[8] In general, recommendations from other clinical guidelines regarding thromboprophylaxis and/or treatment of VTE are in line with the ACCP.[9-11]

Clinical guidelines also recommend the use of LMWH, fondaparinux, UFH, or bivalirudin (a direct thrombin inhibitor) for the management of a non-ST-segment elevated acute coronary syndrome. The use of a specific agent over another is based on individual patient risk factors, as well as the timing and intensity of other planned management strategies. In addition, it appears that fondaparinux has a more favorable safety and efficacy profile compared to LMWH in certain clinical situations, including patients at high-risk for bleeding. While all of the pertinent clinical guidelines recommend LMWH as an appropriate option for anticoagulation, it appears that enoxaparin has the most established evidence for this indication.[12,13] LMWH and fondaparinux are also recommended anticoagulant therapies in acute STEMIs.[14,15]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Dalteparin (Fragmin®)	Injectable anticoagulants/low molecular weight heparin	-
Enoxaparin (Lovenox®*)	Injectable anticoagulants/low molecular weight heparin	✔
Fondaparinux (Arixtra®*)	Injectable anticoagulants/factor Xa inhibitors	✔

*Generic available in at least one dosage form or strength.

Indications

In general, the injectable anticoagulants are Food and Drug Administration-approved for prophylaxis and/or treatment of venous thromboembolism.[1-3] Of the agents in the class, enoxaparin currently is approved for the greatest number of unique indications, and is the only injectable anticoagulant to be approved for the treatment of acute ST-segment elevation myocardial infarction.[2] Both enoxaparin and dalteparin are approved for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarctions.[1,2] Dalteparin is also the only low molecular weight heparin agent that is not approved for the treatment of venous thromboembolism, yet it is the only agent in the class that is approved for the extended treatment of symptomatic venous thromboembolism in patients with cancer.[1]

Table 2. Food and Drug Administration Approved Indications[1-4]

Indication	Dalteparin	Enoxaparin	Fondaparinux
Extended treatment of symptomatic venous thromboembolism (proximal deep vein thrombosis and/or pulmonary embolism) in patients with cancer	✔*		
Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction	✔†	✔†	
Prophylaxis of deep vein thrombosis‡			
• Medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness	✔	✔	
• Patients undergoing abdominal surgery who are at risk for thromboembolic complications	✔	✔	✔
• Patients undergoing hip fracture surgery			✔§
• Patients undergoing hip replacement surgery	✔	✔‖	✔
• Patients undergoing knee replacement surgery		✔	✔
Treatment of acute deep vein thrombosis		✔¶	✔#
Treatment of acute pulmonary embolism			✔**
Treatment of acute ST-segment elevation myocardial infarction		✔††	

*In these patients therapy begins with the initial venous thromboembolism treatment and continues for six months.
†When concurrently administered with aspirin therapy.
‡Which may lead to pulmonary embolism.
§Including extended prophylaxis.
‖During and following hospitalization.
¶Indicated for inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin, and for outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin.
#When administered in conjunction with warfarin.
**When administered in conjunction with warfarin when initial therapy is administered in the hospital.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction receiving thrombolysis and being managed medically or with percutaneous coronary intervention.

Pharmacokinetics

Table 3. Pharmacokinetics[1-3]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dalteparin	87	Major (% not reported)	Not reported	3 to 5
Enoxaparin	100	40	Not reported	7
Fondaparinux	100	50 to 77	Not reported	13 to 21

Clinical Trials

The evidence demonstrating the safety and efficacy of the injectable anticoagulants in Food and Drug Administration-approved indications is well established, and as mentioned previously, clinical guidelines support the use of these agents for these indications.[8-15,16-74] Due to the fact that patients experiencing an acute coronary syndrome will receive treatment with an injectable anticoagulant in an acute hospital setting, only meta analyses and Cochrane Reviews demonstrating the safety and efficacy in this setting are included in Table 4.[16-20] These sources plus individual randomized-controlled trials evaluating the individual injectable anticoagulants for the treatment and/or prevention of venous thromboembolism (VTE), or thromboprophylaxis, have been included.[21-73] It can be assumed that for this indication, treatment is more likely to be administered as an outpatient, as recommended per current clinical guidelines.[8]

Currently, dalteparin is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing dalteparin to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with dalteparin at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow-up revealed a significant benefit in mortality with dalteparin in patients without known metastases of their cancer.[21,22] A Cochrane Review that included 16 randomized-controlled trials of cancer patients receiving initial treatment for VTE compared therapy with a low molecular weight heparin (LMWH) agent, unfractionated heparin (UFH), and fondaparinux. Results suggest that LMWH agents may be “superior” to UFH for the initial treatment of VTE in cancer patients due to an observed nonsignificant advantage of these agents for reducing the incidence of recurrent VTE. No difference was observed when treatment with a LMWH agent was compared to fondaparinux for reducing the incidence of recurrent VTE, or for the incidence of major and minor bleeding events. This review also compared two individual LMWH agents, dalteparin and tinzaparin, and no differences were observed for any of the outcomes (incidence of VTE or major bleeding). In terms of mortality, the only significant difference among the treatments was between LMWH agents and UFH, which favored treatment with a LMWH agent.[23] Of note, while dalteparin is the only LMWH agent to have approval for the extended treatment of symptomatic VTE in patients with cancer, the American College of Chest Physicians does not distinguish among the various agents in their recommendations for thromboprophylaxis in patients with cancer. In addition, use of routine prophylaxis with LMWH or UFH is suggested against and prophylactic use of vitamin K antagonists are not recommended in outpatients with cancer who have no additional risk factors for VTE.[8]

The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established.[25-74] Several placebo-controlled trials, meta-analyses, and systematic reviews with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing an orthopedic surgery have been conducted and consistently demonstrate their efficacy.[26-29,34-40,55,65,74] When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis which include heparin, UFH, and warfarin, “superiority” in terms of recurrent VTE and safety is not always consistent, which supports recommendations from current clinical guidelines.[30,31,45-53,66-72] For treatment and thromboprophylaxis in these patients, any of these options may be appropriate; however, LMWH is suggested in preference to the other agents recommended as alternatives.[8] Enoxaparin has also been compared head-to-head with the oral anticoagulant rivaroxaban (Xarelto®) for prophylaxis of deep vein thrombosis in a global program of clinical trials known collectively

as Regulation in Orthopedic Surgery to Prevent Deep Vein thrombosis and Pulmonary Embolism (RECORD). The RECORD program consists of four individual trials (RECORD1, 2, 3 and 4) evaluating the safety and efficacy of rivaroxaban for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries. Primary and secondary endpoints were similar among the four trials and major bleeding was defined as bleeding that was fatal, involved a critical organ or required reoperation, clinically overt bleeding outside the surgical site that was associated with a decrease in the hemoglobin level of at least 2 g/dL, or a bleed requiring an infusion of two units or more of blood.[41-44]

RECORD1 (N=4,541) and RECORD2 (N=2,509) were two, large, double-blind, multicenter, randomized-controlled trials evaluating rivaroxaban for thromboprophylaxis in patients undergoing hip replacement surgery. Both trials compared rivaroxaban 10 mg once-daily to enoxaparin 40 mg once-daily. In RECORD1 rivaroxaban and enoxaparin were both administered for 35 days, while in RECORD2 rivaroxaban was administered for 31 to 39 days (extended thromboprophylaxis) and enoxaparin was administered for 10 to 14 days.[41,42] In RECORD1, the risk of the primary composite endpoint of any deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause up to 36 days was significantly reduced with rivaroxaban compared to enoxaparin (1.1 vs 3.7%; absolute risk reduction [ARR], -2.6%; 95% confidence interval [CI], -3.7 to -1.5; *P*<0.001). Treatment with rivaroxaban also significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to -1.0; *P*<0.001).[41] Rivaroxaban had no beneficial effect on all-cause mortality (on-treatment: 0.3 vs 0.3%; *P*=1.00, follow-up: 0.1 vs 0.0%; *P*=1.00). The rate of major bleeding was similar between rivaroxaban and enoxaparin (0.3 vs 0.1%; *P*=0.18). In addition, rivaroxaban and enoxaparin had similar rates of any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and hemorrhagic wound complications (1.5 vs 1.7%; *P* value were not reported).[41] In RECORD2, rivaroxaban significantly reduced the risk of the primary composite endpoint up to 30 to 42 days (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). In this trial, the risk of major VTE was also significantly reduced with rivaroxaban (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban again demonstrated no beneficial effects on all-cause mortality (0.2 vs 0.7%; *P*=0.29). Similar to RECORD1, there were no differences between rivaroxaban and enoxaparin in the rates of major bleeding, any on-treatment nonmajor bleeding, and hemorrhagic wound complications (*P* values not reported).[42]

Enoxaparin and rivaroxaban were evaluated head-to-head for thromboprophylaxis in patients undergoing knee replacement surgery in the RECORD3 (N=2,531) and RECORD4 (N=3,148) trials. Similar to RECORD1 and RECORD2, these were large, double-blind, double-dummy, multicenter, randomized-controlled trials. The trials compared rivaroxaban 10 mg once-daily to either enoxaparin 40 mg once-daily (RECORD3) or 30 mg twice-daily (RECORD4) for 10 to 14 days. Again, all primary and secondary endpoints were similar to RECORD1 and RECORD2. Furthermore, results from all four trials were consistent.[41,42] In RECORD3, rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin up to 17 days (9.6 vs 18.9%; absolute risk difference [ARD], -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). Rivaroxaban also significantly reduced the rate of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01) and was not associated with any mortality benefit (*P*=0.21). The rates of major bleeding (*P*=0.77) and any on-treatment bleeding (*P*=0.93) were similar between rivaroxaban and enoxaparin, as well as the rate of hemorrhagic wound complications (*P* value not reported).[43] RECORD4 demonstrated similar results, except in this trial, there was no difference between rivaroxaban and enoxaparin in the rate of major VTE (*P*=0.1237).[44] As previously stated, LMWH is suggested in preference to the other agents recommended as alternatives for thromboprophylaxis for orthopedic patients.[8]

Although data comparing the LMWH agents to fondaparinux has not demonstrated significant "superiority" for one therapy in all outcomes, treatment with fondaparinux appears to be associated with a lower incidence of VTE, and a comparable incidence of major bleeding compared to enoxaparin.[57-60] In a meta-analysis of randomized-controlled trials comparing fondaparinux to LMWH therapy (enoxaparin), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with fondaparinux.[61] Another trial noted no difference between fondaparinux and dalteparin for the incidence of VTE and major bleeding.[56]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Coronary Syndrome				
Antman et al[16] Acute phase: Enoxaparin vs UFH Outpatient phase: Enoxaparin vs placebo	MA (2 RCTs) Patients with unstable angina/non-Q-wave MI	N=not reported 43 days (median duration of acute treatment with enoxaparin and UFH were 4.6 and 2.6 days, and 3.0 and 2.6 days)	Primary: All-cause mortality, recurrent MI, urgent revascularization, major hemorrhage Secondary: Not reported	Primary: The composite end point of death or nonfatal MI was consistently about 20% lower at all time points in enoxaparin-treated patients. Significance for the reduction in the endpoint was observed at day eight (OR, 0.77; 95% CI, 0.62 to 0.95; *P*=0.02) and persisted through days 14 (OR, 0.79; 95% CI, 0.65 to 0.96; *P*=0.02) and 43 (OR, 0.82; 95% CI, 0.69 to 0.97; *P*=0.02). The absolute difference in event rates for death or nonfatal MI between the pooled UFH- and enoxaparin-treated patients increased from 1.2% at day eight to 1.5% at day 43. A significant treatment benefit of enoxaparin on the composite end point of death, nonfatal MI and urgent revascularization was observed at day two (OR, 0.77; 95% CI, 0.63 to 0.94; *P*=0.012) and persisted through days 43 (OR, 0.80; 95% CI, 0.71 to 0.91; *P*=0.0005). The absolute difference in pooled event rates widened from 1.4% at day two to 3.2% at day 43. Beginning at day eight, a trend toward a lower mortality rate was observed in the pooled enoxaparin-treated patients (OR, 0.80; 95% CI, 0.56 to 1.16) and persisted through day 43 (OR, 0.84; 95% CI, 0.66 to 1.08). During acute treatment, the pooled rate of major hemorrhage was 1.3 and 1.1% in the enoxaparin- and UFH-treated patients (OR, 1.23; 95% CI, 0.80 to 1.89; *P*=0.35). The pooled rate of minor hemorrhage was 10.0 and 4.3% of enoxaparin- and UFH-treated patients (OR, 2.38; 95% CI, 1.98 to 2.85; *P*<0.0001). Secondary: Not reported
Murphy et al[17] Enoxaparin vs	MA (12 RCTs) Patients with STEMI or NSTE ACS	N=49,088 30 days	Primary: Composite of death, nonfatal MI or nonfatal major bleeding by 30	Primary: The composite endpoint of death or nonfatal MI was significantly reduced among enoxaparin-treated patients (9.8 vs 11.4%; OR, 0.84; 95% CI, 0.76 to 0.92; *P*<0.001). The composite endpoint of death, nonfatal MI or nonfatal major bleeding was also significantly reduced among enoxaparin-treated patients (12.5

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
UFH			days (or the closest time point available to 30 days) Secondary: The individual endpoints of the composite endpoint	vs 13.5%; OR, 0.90; 95% CI, 0.81 to 1.033; *P*=0.051). For the STEMI cohort, the composite endpoint rate was significantly reduced among enoxaparin-treated patients (11.1 vs 12.9%; OR, 0.84; 95% CI, 0.73 to 0.97; *P*=0.018), but not in the NSTE ACS cohort (14.1 vs 14.3%; OR, 0.97; 95% CI, 0.86 to 1.09; *P*=0.607). Secondary: Mortality was not significantly different between the two treatments (5.0 vs 5.3%; OR, 0.94; 95% CI, 0.87 to 1.02; *P*=0.14); MI was significantly lower (5.5 vs 6.9%; OR, 0.75; 95% CI, 0.65 to 0.86; *P*<0.001) and major bleeding was significantly higher (4.3 vs 3.4%; OR, 1.25; 95% CI, 1.04 to 1.50; *P*=0.019) among enoxaparin-treated patients. Results were similar in the STEMI cohort (mortality: 6.6 vs 7.1%; OR, 0.92; 95% CI, 0.84 to 1.01; *P*=0.097; MI: 3.4 vs 5.1%; OR, 0.64; 95% CI, 0.52 to 0.78; *P*<0.001 and major bleeding: 2.6 vs 1.8%; OR, 1.45; 95% CI, 1.23 to 1.72; *P*<0.001). Death and MI occurred in 9.6 and 11.7% of enoxaparin- and UFH-treated patients (OR, 0.78; 95% CI, 0.67 to 0.91; *P*=0.002). In the NSTE ACS patients, there was no difference in mortality (3.0 vs 3.0%; OR, 0.99; 95% CI, 0.83 to 1.18; *P*=0.890). MI was significantly reduced among enoxaparin-treated patients (8.0 vs 9.1%; OR, 0.87; 95% CI, 0.79 to 0.96; *P*=0.005), as was the composite of death or nonfatal MI (10.0 vs 11.0%; OR, 0.90; 95% CI, 0.81 to 0.996; *P*=0.043). Major bleeding did not differ between the two treatments (6.3 vs 5.4%; OR, 1.13; 95% CI, 0.84 to 1.54; *P*=0.419).
Magee et al[18] LMWH vs UFH	SR (7 RCTs) Patients >18 years of age presenting with ACS requiring treatment within	N=11,092 >14 days (assessments at <48 hours, 3 to 14 days and >14 days)	Primary: Death, MI, recurrent angina, revascularization procedures, major hemorrhage, minor	Primary: Overall, treatment with LMWH did not reduce the incidence of death compared to UFH for any of the time periods. The pooled data for all three periods demonstrated the risk of death to be similar between the two treatments (RR, 1.00; 95% CI, 0.69 to 1.44). Treatment with LMWH was “superior” in preventing MI (RR, 0.83; 95% CI, 0.70 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	72 hours of presentation		hemorrhage, thrombocytopenia, allergic reactions Secondary: Not reported	0.99) when data were pooled from all time periods. For the individual time periods, LMWH was "superior" in preventing MI (RR, 0.83; 95% CI, 0.69 to 0.99) at three to 14 days, and no difference was found at the early phase (<48 hours) or at the last phase (≥30 days). Overall, the incidence of MI was 4.2 vs 5.0% for enoxaparin- and UFH-treated patients. Given the risk difference of 0.008, 125 patients would require treatment with LMWH to prevent one additional MI. Over all the time periods, LMWH tended to reduce episodes of recurrent angina compared to UFH (RR, 0.83; 95% CI, 0.68 to 1.02). Seven trials reported revascularization procedures within two weeks of admission to the hospital (n=11,128). LMWH-treated patients experienced significantly fewer revascularization procedures compared to UFH-treated patients (14.2 vs 16.1%; RR, 0.88; 95% CI, 0.82 to 0.95). Given the risk difference of 0.02, 50 patients would need to be treated with LMWH to prevent one additional revascularization procedure. Treatment with LMWH was "superior" for the prevention of a combined endpoint of death, MI, recurrent angina or revascularization procedure during the early (<48 hours; (RR, 0.80; 95% CI, 0.67 to 0.95) and sub-acute phase (three to 14 days; RR, 0.80; 95% CI, 0.66 to 0.98). During the sub-acute phase, out of the three LMWH agents described (dalteparin, enoxaparin and, nadroparin*), only enoxaparin appeared better than UFH (RR, 0.85; 95% CI, 0.76 to 0.94). No difference between the two treatments was found at the late phase (≥30 days) (RR, 0.90; 95% CI, 0.80 to 1.01). Overall, the incidence of the combined endpoint was 12.5 vs 14.1% in enoxaparin- and UFH-treated patients. Given the risk difference of 0.02, the NNT with LMWH is 50 to prevent one event. There was no difference in major bleeds between the two treatments (RR, 1.00; 95% CI, 0.80 to 1.24). LMWH-treated patients had a nonsignificant increase in the incidence of minor bleeds (RR, 1.40; 95% CI, 0.68 to 2.90). Thrombocytopenia was a relatively rare event in the four trials that reported this

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				outcome, occurring in only 1.5% of all patients. However, LMWH-treated patients had a significant reduction in thrombocytopenia (RR, 0.64; 95% CI, 0.44 to 0.94). Data regarding allergic reactions was not reported. Secondary: Not reported
Malhotra et al (abstract)[19] LMWH (excluding enoxaparin) vs UFH	MA (5 RCTs) Patients with unstable angina	N=not reported Duration not reported	Primary: Composite of death, MI, recurrent angina and urgent revascularization; composite of major hemorrhage, minor hemorrhage, thrombocytopenia, allergic reaction and any other adverse event Secondary: Not reported	Primary: LMWH-treated patients had a nonsignificant reduction in the incidence of the composite efficacy endpoint (OR, 0.83; 95% CI, 0.70 to 0.99; *P*=0.08). The OR for the safety data was 0.78 (95% CI, 0.69 to 1.26; *P*=0.33). Secondary: Not reported
Eikelboom et al[20] UFH vs LMWH vs	MA (12 RCTs) Patients with unstable angina or non-Q-wave MI, receiving aspirin	N=17,157 Duration varied (short and long term treatment)	Primary: Composite of death or MI, major bleeding Secondary: Recurrent angina, need for revascularization	Primary: *Short term UFH vs placebo or no treatment* Pooled analysis from six trials (n=1,353) revealed that treatment with short term UFH had a significant 33% reduction in the risk of death or MI during the first week of treatment (OR, 0.67; 95% CI, 0.45 to 0.99; *P*=0.045). The reduction was accounted for almost entirely by a reduction in nonfatal MI. Short term UFH had a nonsignificant risk of major bleeding (OR, 1.88; 95% CI, 0.60 to 5.87; *P*=0.28). *Short term LMWH vs placebo or no treatment* Pooled analysis from two trials (n=1,639) revealed that overall, treatment with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or no treatment				short term LMWH had a 66% reduction in the risk of death or MI (OR, 0.34; 95% CI, 0.20 to 0.58; *P*<0.0001). Short term LMWH had a nonsignificant 48% increase in the risk of major bleeding (OR, 1.48; 95% CI, 0.45 to 4.84; *P*=0.51). *Short term UFH and LMWH vs placebo or no treatment* When the results of all the short term trials were combined (six trials; n=2,992), treatment with short term UFH and LMWH had a significant 47% reduction in the risk of death or MI (OR, 0.53; 95% CI, 0.38 to 0.73; *P*=0.0001). This is equivalent to preventing 29 events (death or MI) for every 1,000 patients treated. When the data on bleeding was combined, short term treatment had a nonsignificant increase in the risk of major bleeding (OR, 1.41; 95% CI, 0.62 to 3.23). *Short term LMWH vs UFH* Pooled analysis from five trials (n=12,171) revealed that after completion of an equal duration of treatment, short term LMWH had a nonsignificant 12% reduction in the risk of death or MI (OR, 0.88; 95% CI, 0.69 to 1.12; *P*=0.34). There was no difference in the risk of major bleeding between the two treatments (OR, 1.00; 95% CI, 0.64 to 1.57; *P*=0.99). *Long term LMWH vs placebo* Pooled analysis of five trials (n=12,099) revealed that treatment with long term (<90 days) LMWH had no reduction on the risk of death or MI (OR, 0.98; 95% CI, 0.81 to 1.17; *P*=0.80). Long term LMWH had a significant increase in the risk of major bleeding (OR, 2.26; 95% CI, 1.63 to 3.14; *P*<0.0001), which is equivalent to an excess of 12 major bleeds for every 1,000 patients treated. Secondary: *Short term UFH vs placebo or no treatment* Treatment with short term UFH did not significantly reduce the incidence of recurrent angina (OR, 0.94; 95% CI, 0.58 to 1.54; *P*=0.81) or revascularization procedures (OR, 1.25; 95% CI, 0.76 to 2.06; *P*=0.37) in trials that reported these outcomes separately. *Short term LMWH vs placebo or no treatment* Recurrent angina was not reported separately in one of the trials, but pooled

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				analysis on revascularization reveals that short term LMWH had a significant 72% reduction (OR, 0.28; 95% CI, 0.12 to 0.66; *P*=0.003) during the first five to seven days of therapy (four vs 18 events). *Short term LMWH vs UFH* Pooled analysis from three trials (n=not reported) revealed that short term treatment with LMWH had a borderline significant 16% reduction (OR, 0.84; 95% CI, 0.71 to 1.00; *P*=0.05) in the risk of recurrent angina, but there was no difference between the two treatments in the need for revascularization (OR, 0.96; 95% CI, 0.75 to 1.24; *P*=0.77). *Long term LMWH vs placebo* Pooled analysis of five trials (n=12,099) revealed that long term treatment with LMWH did not significantly reduce the risk of recurrent angina (OR, 1.12; 95% CI, 0.85 to 1.49; *P*=0.42) or need for revascularization (OR, 0.89; 95% CI, 0.75 to 1.05; *P*=0.16).
Extended Treatment of Symptomatic Venous Thromboembolism in Patients with Cancer				
Lee et al[21] Dalteparin 200 units/kg SC QD for 1 month, followed by 150 units/kg SC QD vs warfarin or acenocoumarol*, dose adjusted to maintain an INR of 2.5 Patients receiving an oral anticoagulant received dalteparin initially for five to seven days.	DB, MC, RCT Adult patients with active cancer and newly diagnosed cancer with symptomatic proximal DVT, PE or both	N=676 6 months	Primary: First episode of symptomatic, recurrent DVT, PE or both Secondary: Clinically overt bleeding, death	Primary: Symptomatic, recurrent DVT, PE or both occurred in 27 out of 336 and 53 out of 336 dalteparin- and oral anticoagulant-treated patients (HR, 0.48; 95% CI, 0.30 to 0.77; *P*=0.002). All recurrent DVTs were proximal. Secondary: Six (19 out of 338) vs 4% (12 out of 335) of dalteparin- and oral anticoagulant-treated patients had major bleeding (*P*=0.27). The respective rates of any bleeding were 14 and 19% (*P*=0.09). During the six month period, 130 and 136 dalteparin- and oral anticoagulant-treated patients died. The respective mortality rates were 39 and 41% (*P*=0.53). Ninety percent of the deaths in each group were due to progressive cancer.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lee et al[22] Dalteparin 200 units/kg SC QD for 1 month, followed by 150 units/kg SC QD vs warfarin or acenocoumarol*, dose adjusted to maintain an INR of 2.5 Patients receiving an oral anticoagulant received dalteparin initially for five to seven days.	Post hoc analysis of Lee et al[21] Adult patients with active cancer and newly diagnosed cancer with symptomatic proximal DVT, PE or both	N=676 12 month follow up	Primary: Survival data Secondary: Not reported	Primary: During the 12 month follow up period, 174 out of 296 and 182 out of 306 dalteparin- and oral anticoagulant-treated patients died (*P*=0.62). In patients without known metastases, 15 out of 75 and 26 out of 75 dalteparin- and oral anticoagulant-treated patients died. The estimate of the probability of death at 12 months was 20 vs 36% in dalteparin- and oral anticoagulant-treated patients (HR, 0.50; 95% CI, 0.27 to 0.95; *P*=0.03). In patients with known metastatic malignancy, 159 out of 221 and 156 out of 231 dalteparin- and oral anticoagulant-treated patients died (probability of mortality at 12 months, 72 vs 69%; HR, 1.1; 95% CI, 0.87 to 1.4; *P*=0.46). A comparison of the two HRs of dalteparin and oral anticoagulants between the subgroups of patients with and without metastatic disease was significant (*P*=0.02). Secondary: Not reported
Akl et al[23] LMWH vs UFH vs fondaparinux A total of 16 RCTs were included: 13 comparing LMWH to UFH, two comparing fondaparinux	SR (16 RCTs) Patients with cancer with a confirmed diagnosis of VTE receiving initial treatment for VTE	N=1,506 Duration varied	Primary: Mortality Secondary: Symptomatic recurrent DVT, symptomatic recurrent PE, major bleeding, minor bleeding, postphlebitic syndrome, quality of life, thrombocytopenia	Primary: *LMWH vs UFH* The number of fatal events were available for 11 trials at three months follow up and revealed treatment with LMWH had a significant reduction in mortality (RR, 0.71; 95% CI, 0.52 to 0.98). *Fondaparinux vs UFH* Pooled analysis revealed no difference in mortality between the two treatments (RR, 1.27; 95% CI, 0.88 to 1.84). *Dalteparin vs tinzaparin* No difference in mortality was observed between the two treatments (RR, 0.86; 95% CI, 0.43 to 1.73). Secondary: *LMWH vs UFH*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to heparin and one comparing dalteparin to tinzaparin.				No data was available for DVT or PE events separately, but data for recurrent VTE events were available for three trials. Pooled analysis revealed that treatment with LMWH had a nonsignificant reduction in the risk of recurrent VTE (RR, 0.78; 95% CI, 0.29 to 2.08). No data were available for bleeding outcomes, postphlebitic syndrome, quality of life or thrombocytopenia. *Fondaparinux vs UFH* Pooled analysis revealed no difference in the risk of recurrent VTE (RR, 0.95; 95% CI, 0.57 to 1.60), major bleeding (RR, 0.79; 95% CI, 0.39 to 1.63) or minor bleeding (RR, 1.50; 95% CI, 0.87 to 2.59) between the two treatments. No data were available for postphlebitic syndrome, quality of life and thrombocytopenia. *Dalteparin vs tinzaparin* No difference in the risk of recurrent VTE (RR, 0.44; 95% CI, 0.09 to 2.16), major bleeding (RR, 2.19; 95% CI, 0.20 to 23.24) or minor bleeding (RR, 0.82; 95% CI, 0.30 to 2.21) was observed between the two treatments. No data were available for postphlebitic syndrome, quality of life and thrombocytopenia.
Di Nisio et al[24] Any oral or parenteral anticoagulant (UFH, LMWH, VKA, direct thrombin or factor Xa inhibitors), or both vs inactive control (placebo, no treatment, standard care) or active control	SR (9 RCTs) Ambulatory outpatients of any age with either a solid or hematological cancer, at any stage, and receiving chemotherapy, without a positive history of VTE	N=3,538 Duration varied	Primary: Symptomatic VTE, major bleeding Secondary: Symptomatic PE, symptomatic DVT, asymptomatic VTE, overall VTE, minor bleeding, one year overall mortality, arterial thromboembolic events, superficial thrombophlebitis, quality of life, number of patients experiencing any	Primary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that when compared to placebo, LMWH was associated with a significant reduction symptomatic VTE (RR, 0.62; 95% CI, 0.41 to 0.93), corresponding to a NNT of 60. Pooled analysis of six RCTs suggested a 60% increased risk of a major bleeding (RR, 1.57; 95% CI, 0.69 to 3.60). *LMWH vs active control* In one trial, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR, 0.33; 95% CI, 0.14 to 0.83) while the difference with aspirin was not significant (RR, 0.50; 95% CI, 0.19 to 1.31). In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of major bleeding. *VKA vs inactive control*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			serious adverse event	In one trial, a trend for a reduction in symptomatic VTE (RR, 0.15; 95% CI, 0.02 to 1.20) was reported. There was no significant effect on major bleeding (RR, 0.52; 95% CI, 0.05 to 5.71). *VKA vs active control* One trial reported a nonsignificant difference between VKA and aspirin (RR, 1.50; 95% CI, 0.74 to 3.04). *Antithrombin vs inactive control* In one trial, the effects of antithrombin on symptomatic VTE (RR, 0.84; 95% CI, 0.41 to 1.73) and major bleeding (RR, 0.78; 95% CI, 0.03 to 18.57) were not significant. Secondary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that there was no significant effect on symptomatic PE (RR, 0.63; 95% CI, 0.21 to 1.91) or DVT (RR, 0.60; 95% CO. 0.33 to 1.07). In pooled data from six RCTs, the risk of overall VTE was reduced by 45% with LMWH (RR, 0.55; 95% CI, 0.34 to 0.88) whereas there was no significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis, or serious adverse events. None of the six trials considered quality of life, heparin-induced thrombocytopenia, or the incidence of osteoporosis as study incomes. Three trials reported on symptomatic VTE and major bleeding in patient with non-small cell or small cell lung cancer, or both. Pooled analysis showed a nonsignificant 46% reduction in symptomatic VTE (RR, 0.54; 95% CI, 0.27 to 1.09) and a nonsignificant 73% higher risk of major bleeding with LMWH compared to control (RR, 1.73; 95% CI, 0.65 to 4.57). *LMWH vs active control*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of symptomatic PE or DVT, minor bleeding, and symptomatic arterial thromboembolism. *VKA vs inactive control* In one trial, there was no significant effect on symptomatic PE (RR, 1.05; 95% CI, 0.07 to 16.58), symptomatic DVT (RR, 0.08; 95% CI, 0.00 to 1.42), or minor bleeding (RR, 2.44; 95% CI, 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in the VKA or placebo groups. *VKA vs active control and antithrombin vs inactive control* Secondary outcomes were not reported for these comparisons.
Prophylaxis and/or Treatment of Venous Thromboembolism				
Douketis et al[25] Dalteparin 5,000 units SC QD	MC, OL, PRO, single-arm Patients ≥18 years of age, body weight >45 kg, expected intensive care unit length of stay >72 hours and severe renal insufficiency	N=156 Up to 30 days	Primary: DVT, bleeding, HIT, creatinine clearance Secondary: Not reported	Primary: Seven (5.1%) patients (95% CI, 2.5 to 10.2) developed DVT, which was asymptomatic and involved the proximal leg veins in all patients. No patient developed PE. Ten (7.2%) patients (95% CI, 4.0 to 12.8) developed major bleeding, two of whom died from bleeding. Two (1.4%) patients (95% CI, 0.4 to 5.1) with prior exposure to UFH had serologically confirmed HIT. Mean (SD) creatinine clearance at baseline and at the end of dalteparin prophylaxis was 18.9 (6.4) and 28.4 (17.3) mL/minute, respectively (*P* value not reported). Secondary: Not reported
Michot et al[26] Dalteparin 2,500 units SC once, followed by 2,500 to 5,000 units SC QD	PRO, RCT, SB Patients 18 to 80 years of age referred to an	N=218 Up to 30 days	Primary: Incidence of DVT, safety Secondary:	Primary: Lower limb DVT was diagnosed in 10 (15.6%) and one (1.5%) patient(s) in no treatment and dalteparin-treated patients (*P*=0.004). No major bleeding episodes occurred with either treatment during the trial period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no treatment Patients in the control group were given no medical prophylaxis against thromboembolism.	institution for diagnostic or therapeutic arthroscopic knee surgery as outpatients		Not reported	Minor complications involved soft-tissue hemorrhage elsewhere than at the injection site (four vs three patients) or immediate post-operative knee swelling (four vs one patients) (*P* values not significant). Secondary: Not reported
Lassen et al[27] Dalteparin vs placebo All patients received dalteparin 5,000 units SC QD for seven days after the surgery.	DB, PG, PRO, RCT Patients >18 years of age admitted to the hospital for total hip arthroplasty	N=300 35 days	Primary: DVT, safety Secondary: Not reported	Primary: A total of 17 patients developed DVT during the trial, giving a total rate of DVT of 8% of which five (29%) were symptomatic. Fifteen out of 182 patients (8.2%; 95% CI, 4.3 to 12.2) undergoing primary operation developed DVT, and two out of 33 patients (6.1%; 95% CI, 0.0 to 14.2) undergoing revision arthroplasty (*P* value not significant). The analysis revealed that treatment with dalteparin had a significant 63% RRR in the risk of total DVT (*P*=0.039). Prolonged prophylaxis with dalteparin reduced the risk of postoperative DVT by 63%. No significant difference was revealed in terms of transfusion requirements, hemoglobin counts, hematocrit counts and platelet counts between the two treatments. Adverse events were reported in 58 and 53 dalteparin- and placebo-treated patients (*P* value not significant). Serious adverse events were slightly less frequent in the dalteparin-treated patients (2.9 vs 6.4%; *P* value not significant). Secondary: Not reported
Leizorovicz et al[28] Dalteparin 5,000 units SC QD	DB, MC, PC, RCT Patients ≥40 years of age with	N=2,991 14 days	Primary: Incidence of VTE and sudden death by day 21	Primary: The incidence of the primary endpoint was 2.77 and 4.96% in dalteparin- and placebo-treated patients, a risk reduction of 45% (RR, 0.55; 95% CI, 0.38 to 0.80; *P*=0.0015).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	an acute medical condition requiring a projected hospitalization of ≥4 days and had ≤3 days of prior immobilization		Secondary: All-cause mortality by days 14, 21 and 90; objectively verified symptomatic DVT or asymptomatic proximal DVT by day 21; major and minor bleeding, drug-related allergic reactions and thrombocytopenia by day 21; symptomatic VTE at day 90	Two placebo and no dalteparin-treated patients had a fatal PE by day 21 (RR, 0.00). Sudden death by day 21 occurred in five and three dalteparin- and placebo-treated patients (0.27 vs 0.17%; RR, 1.65; 95% CI, not reported). Secondary: All-cause mortality in dalteparin- and placebo-treated patients by days 14, 21 and 90 are as follows: 0.43 vs 0.38% (RR, 1.13; 95% CI, 0.41 to 3.12), 2.35 vs 2.32% (RR, 1.01; 95% CI, 0.66 to 1.54) and 6.12 vs 6.01% (RR, 1.02; 95% CI, 0.78 to 1.33). The rate of objectively verified symptomatic DVT or asymptomatic proximal DVT by day 21 in dalteparin- and placebo-treated patients was 2.12 vs 4.37% (RR, 0.49; 95% CI, 0.32 to 0.74). By day 21, major bleeding had occurred in 12 patients; nine (0.49%) and three (0.16%) dalteparin- and placebo-treated patients (*P*=0.15). Two and one dalteparin- and placebo-treated patient(s) died of hemorrhage. There was no difference in the proportion of patients who reported at least one adverse event between the two treatments (39.7 vs 39.8%, respectively). The rate of symptomatic VTE by day 90 in dalteparin- and placebo-treated patients was 0.93 vs 1.33% (RR, 0.70; 95% CI, 0.36 to 1.35).
Torholm et al[29] Dalteparin 2,500 units SC QD twice, followed by 5,000 units SC QD vs placebo	PC, RCT Patients >40 years of age admitted for total hip replacement	N=112 7 days	Primary: DVT, safety Secondary: Not reported	Primary: DVT developed in 28 patients; nine (16%) and 19 (35%) dalteparin- and placebo-treated patients (*P*<0.02). A higher number of DVTs occurred during the first four postoperative days than in the remaining study period for placebo-treated patients (*P*<0.02). Such a difference was not found in dalteparin-treated patients. No difference with respect to preoperative and postoperative bleeding, hemoglobin concentration before and one week after operation or blood transfusion requirements was observed between the two treatments. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Francis et al[30] Dalteparin 2,500 units SC twice, followed by 5,000 units SC QD until venography was performed vs warfarin, dosing varied	RCT Patients ≥18 years of age who were scheduled to have a unilateral primary or revision total hip arthroplasty	N=580 Duration not reported	Primary: DVT, bleeding Secondary: Not reported	Primary: DVT developed in 28 out of 192 (15%) and 49 out of 190 (26%) dalteparin- and warfarin-treated patients (*P*=0.006). The prevalence of proximal DVT was nonsignificantly lower in dalteparin-treated patients (5 vs 8%; *P*=0.185). No difference was observed in the measured blood loss between the two treatments, either on the day of the operation or in the postoperative period. Major bleeding complications occurred in six (2%) and four (1%) of dalteparin- and warfarin-treated patients. No difference was observed in the frequency of other bleeding complications, including minor bleeding in the gastrointestinal or urinary tract and hematoma at the site injection between the two treatments (*P*=0.28). Secondary: Not reported
Eriksson et al[31] Dalteparin 5,000 units SC QD vs UFH 5,000 units SC QD	DB, PRO, RCT Patients ≥40 years of age undergoing elective total hip replacement	N=136 12±2 days (10 days of treatment)	Primary: Thromboembolic complications, bleeding complications, mortality, adverse events Secondary: Not reported	Primary: On day 12±2 days, DVT was diagnosed in 44 patients; 19 (30.2%; 95% CI, 19.2 to 43.0) dalteparin-treated patients vs 25 (42.4%; 95% CI, 29.6 to 55.9) UFH-treated patients. The difference in the total rate of thrombosis between the two treatments was not significant (95% CI, -4.7 to 29.2; *P*=0.189). For 127 patients, PE was detected in 27 of them; eight (12.3%; 95% CI, 5.5 to 22.8) dalteparin-treated patients vs 19 (30.6%; 95% CI, 19.6 to 43.7) UFH-treated patients. PE occurred significantly more frequently in UFH-treated patients (95% CI, 4.4 to 32.3; *P*=0.016). Transient minor bleeding complications, which were equally distributed between the two treatments, consisted of minor epistaxis in two patients, suspected hematemesis in one patient, melena in one patient and hemorrhoidal bleeding in two patients. One UFH-treated patient had a minor cerebral infarction with transient hemiplegia. One UFH-treated patient died from a cardiac infarction on the sixth postoperative day, but neither DVT nor PE was detected.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In two UFH-treated patients, signs of SQ infection of the wound developed. Thrombocytopenia was not identified in any patient. Secondary: Not reported
Krotenberg et al[32] Dalteparin vs enoxaparin	RETRO Patients who underwent total knee arthroplasty or total hip arthroplasty and received enoxaparin, dalteparin or aspirin as DVT prophylaxis at the institution where their total knee arthroplasty or total hip arthroplasty was performed and who received enoxaparin or dalteparin as DVT prophylaxis during their rehabilitation stay	N=934 Duration not reported	Primary: DVT, bleeding Secondary: Not reported	Primary: A total of three and one DVT event(s) occurred in enoxaparin- and dalteparin-treated patient(s). The age-adjusted risk of a DVT event among dalteparin-treated patients was nonsignificantly less than that among enoxaparin-treated patients (OR, 0.016; 95% CI, 0.016 to 1.570). A total of six and seven bleeding events occurred in enoxaparin- and dalteparin-treated patients. All events were minor and did not require transfusions or transfer to an acute care facility. The age-adjusted risk of a bleeding event among dalteparin-treated patients was nonsignificantly less than that among enoxaparin-treated patients (OR, 0.634; 95% CI, 0.209 to 1.922). Secondary: Not reported
Spiro et al[33] Enoxaparin 10 mg SC QD vs	DB, MC, PG, RCT Patients ≥31 years of age who were scheduled	N=572 7 days	Primary: Venous thrombosis by day seven, hemorrhagic complications	Primary: The incidence of DVT was 25, 14 and 11% among patients receiving enoxaparin 10, 40 and 30 mg, respectively. A significantly higher incidence of DVT occurred with 10 mg compared to either 40 mg (OR, 2.16; 95% CI, 1.21 to 4.10; *P*=0.02) or 30 mg (OR, 2.93; 95% CI, 1.48 to 5.81; *P*<0.001). There was no difference in the incidence of DVT with 30 mg compared to the 40 mg dose (OR, 1.36; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 40 mg SC QD vs enoxaparin 30 mg SC BID	for hip replacement surgery		Secondary: Not reported	0.73 to 2.53; *P*>0.2). The overall incidence of hemorrhagic episodes with enoxaparin 10 mg (5%) was significantly lower than with the 30 mg dose (13%; *P*<0.05). The incidence of hemorrhagic episodes was similar between the 40 and 30 mg doses (11 vs 13%; *P* value not reported). The overall incidence of major hemorrhage was low with all three treatment groups. Secondary: Not reported
Bergqvist et al[34] Enoxaparin 40 mg SC QD vs placebo All patients received enoxaparin 40 mg SC QD for 6 to 10 days before randomization.	DB, PC, PRO, RCT Patients ≥40 years of age with a life expectancy of ≥6 months who were scheduled to undergo abdominal surgery for a malignant tumor	N=609 31 days (19 to 21 days of treatment)	Primary: DVT, occurrence of hemorrhage Secondary: Death from thromboembolic disease before three months, other serious adverse events	Primary: During the DB period, the overall incidence of VTE was 8.4%. In patients who were given one week of prophylaxis (placebo-treated patients), the incidence was 12.0% compared to 4.8% in patients given four weeks of prophylaxis (enoxaparin-treated patients) (95% CI, 10 to 82; *P*=0.02). There were no differences in the incidence of major or minor bleeding during the DB (*P*>0.99 and *P*=0.66) or the two month follow up (*P*>0.99 and *P* value not reported) period between the two treatments. Secondary: There were no deaths during the DB period. Nine patients died during the two month follow up period (three vs six patients receiving enoxaparin and placebo, respectively; *P* value not reported). Among enoxaparin-treated patients, one each died of sepsis, cancer and MI. Among placebo-treated patients, the causes of death were sepsis in two, cancer in three and PE in one. There were no cases of thrombocytopenia, and analysis of other serious adverse events revealed no significant differences between the two treatments.
Hull et al[35] Enoxaparin 40 mg SC QD vs	DB, MC, PG Patients ≥40 years of age with acute medical illness, a life	N=7,500 6 months (28±4 days of treatment)	Primary: VTE, major hemorrhagic complications Secondary:	Primary: At 28±4 days, treatment with enoxaparin significantly reduced the risk of VTE (2.5 vs 4.0%; ARD, -1.53%; 95% CI, -2.54 to -0.52), an effect largely attributable to a decrease in symptomatic DVT (ARD, -0.60%; 95% CI, -1.00 to -0.19). The number of major hemorrhages at 30 days was significantly greater in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients received enoxaparin 40 mg SC QD for 10±4 days before randomization.	expectancy of ≥6 months and had recently reduced mobility for up to 3 days		VTE incidence through three months; mortality at one, three and six months; major and minor hemorrhagic complications, serious adverse events, thrombocytopenia	enoxaparin-treated patients (0.8 vs 0.3%; ARD, 0.51%; 95% CI, 0.12 to 0.89). Secondary: The incidence of VTE observed at 28±4 days was unchanged at 90 days with an additional four and five events in enoxaparin- and placebo-treated patients ARD favoring enoxaparin, -1.57%; 95% CI, -2.61 to -0.53). There was no difference in cumulative all-cause mortality between the two treatments at one, three and six months (*P* values not reported). Treatment with enoxaparin significantly increased the risk of total major and minor bleeding events ARD favoring placebo, 2.37%; 95% CI, 1.26 to 3.48). The proportion of serious adverse events that led to death was 1.3 vs 1.5% in enoxaparin- and placebo-treated patients (*P* value not reported). There was no difference in the incidence of thrombocytopenia between the two treatments (*P* value not reported).
Samama et al[36] Enoxaparin 20 or 40 mg SC QD vs placebo	DD, MC, RCT Medical patients ≥40 years of age, whose projected stay in the hospital was ≥6 days and who were not immobilized for >3 days	N=866 83 to 110 days (6 to 14 days of treatment)	Primary: VTE between days one and 14 Secondary: VTE between days one and 110, death, major and minor hemorrhage, thrombocytopenia, other adverse events	Primary: The incidence of VTE by day 14 was significantly lower in enoxaparin 40 mg-treated patients compared to placebo-treated patients (5.5 vs 14.9%; RR, 0.37; 95% CI, 0.22 to 0.63; *P*<0.001). There was no difference in the primary outcomes between the enoxaparin 20 mg- and placebo-treated patients (*P* value not reported). Secondary: The significant reduction in the incidence of VTE among enoxaparin 40 mg-treated patients was maintained during the three month follow up period. Eight additional VTEs occurred between days 15 and 110. By day 110, 142 patients died; 13.9, 14.7 and 11.4% in placebo-, enoxaparin 20 mg- and enoxaparin 40 mg-treated patients, respectively. The risk of death was nonsignificantly reduced with enoxaparin 40 mg compared to placebo (RR, 0.83; 95% CI, 0.56 to 1.21; *P*=0.31). Similar results were observed with enoxaparin 20 mg (RR, 1.05; 95% CI, 0.71 to 1.56; *P*=0.80).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Major hemorrhage occurred in 11 patients. Among the 31 cases of thrombocytopenia during the treatment period, 14 were considered to be possibly related to treatment (placebo, eight; enoxaparin 20 mg, four; enoxaparin 40 mg, two). There were no differences in the incidence of other adverse events between the enoxaparin and placebo group(s).
Alikhan et al[37] Enoxaparin 20 or 40 mg SC QD vs placebo	Post hoc analysis of Samama et al[34] Medical patients ≥40 years of age, whose projected stay in the hospital was ≥6 days and who were not immobilized for >3 days	N=866 83 to 110 days (6 to 14 days of treatment)	Primary: VTE between days one and 14 Secondary: Not reported	Primary: In patients with NYHA class III or class IV acute heart failure, treatment with enoxaparin had a significant 72% reduction in the primary endpoint (4.0 vs 14.6%; ARR, 10.6%; RR, 0.29; 95% CI, 0.10 to 0.84; *P*=0.02). Patients with an acute respiratory disease had a similar benefit from treatment with enoxaparin 40 mg as those with heart failure with a significant reduction of 75% in the risk of VTE (ARR, 9.8%; RR, 0.25; 95% CI, 0.10 to 0.65; *P*=0.003). Treatment with enoxaparin had a significant 59% reduction in the rate of VTE in patients with an acute infectious diseases (ARR, 9.3%; 95% CI, 0.20 to 0.82; *P*=0.01). Treatment with enoxaparin 40 mg had a significant 72% reduction in the rate of VTE in patients presenting with both acute respiratory and infectious disease (ARR, 11.9%; RR, 0.28; 95% CI, 0.09 to 0.81; *P*=0.02). Treatment with enoxaparin 40 mg had a nonsignificant 52% reduction in the rate of VTE in patients with an acute rheumatic disease (ARR, 10.7%; RR, 0.48; 95% CI, 0.11 to 2.16; *P*=0.4). No differences between male and females or their distribution between the three treatments were observed. Treatment with enoxaparin 40 mg had a significant 78% reduction in the rate of VTE in patients >75 years of age (ARR, 14.4%; RR, 0.22; 95% CI, 0.09 to 0.51;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.0001). Immobilized patients treated with placebo had a VTE incidence rate of 20.3% compared to a rate of 9.0% in enoxaparin-treated patients (RR, 0.44; 95% CI, 0.22 to 0.88; *P*=0.02). Treatment with enoxaparin 40 mg had a nonsignificant 50% reduction in the rate of VTE in patients with cancer (ARR, 9.8%; RR, 0.50; 95% CI, 0.14 to 1.72; *P*=0.4). Treatment with enoxaparin 40 mg had a nonsignificant 51% reduction in the rate of VTE in patients with a previous history of VTE (ARR, 12.2%; RR, 0.49; 95% CI, 0.15 to 1.68; *P*=0.4). Treatment with enoxaparin 40 mg had a nonsignificant 51% reduction in the rate of VTE in obese patients (ARR, 7.7%; RR, 0.49; 95% CI, 0.18 to 1.36; *P*=0.3). Treatment with enoxaparin 40 mg had a significant 76% reduction in the rate of VTE in patients with varicose veins (ARR, 16.2%; RR, 0.24; 95% CI, 0.08 to 0.68; *P*=0.05). Treatment with enoxaparin 40 mg had a significant 74% reduction in the rate of VTE in patients with chronic heart failure (ARR, 8.9%; RR, 0.26; 95% CI, 0.08 to 0.92; *P*=0.04). Secondary: Not reported
Bergqvist et al[38] Enoxaparin vs placebo	DB, PRO, RCT Patients >39 years of age and >60 kg undergoing primary elective hip arthroplasty	N=262 21 days (range, 19 to 23)	Primary: DVT, hemorrhagic complications Secondary: Not reported	Primary: Of the 233 patients who could be evaluated, 18 vs 39% enoxaparin- and placebo-treated patients were diagnosed with a DVT or PE (OR, 2.9; 95% CI, 1.6 to 5.3; *P*<0.001). The frequencies of proximal, indeterminate and distal DVT were as follows: 7 vs 24% (OR, 0.43; 95% CI, 1.90 to 10.00; *P*<0.001), two vs zero percent (OR, not reported; 95% CI, not reported; *P* value not reported) and 13 vs 11% (OR, not reported; 95% CI, not reported; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received enoxaparin 40 SC QD for 7 to 11 days before randomization.				Hematomas were seen at the injection site in one and six placebo- and enoxaparin-treated patients (*P* value not reported). Secondary: Not reported
Planes et al[39] Enoxaparin 40 mg SC QD vs placebo All patients received OL enoxaparin while in the hospital. Randomization to outpatient treatment with enoxaparin or placebo occurred before discharge from the hospital.	DB, PC, RCT Patients ≥45 years of age, bodyweight 45 to 95 kg, who had undergone primary total hip replacement or conversion or revision total hip replacement surgery receiving LMWH prophylaxis for postoperative VTE	N=179 35 days (21 days of treatment)	Primary: DVT, PE Secondary: Onset of proximal or distal DVT	Primary: DVT was detected in 7.1 vs 19.3% of enoxaparin- and placebo-treated patients (*P*=0.018) 19 to 23 days after discharge; corresponding to a risk reduction of 12.2% (95% CI, 2.4 to 22.0) with enoxaparin treatment. By day 21, 17.3% patients in the total population reported symptoms of DVT or had clinical signs that suggested DVT (14 and 16 enoxaparin- and placebo-treated patients; *P* value not reported). There were no deaths or cases of PE during the treatment period. Secondary: There was no difference in the proportion of proximal DVT between the two treatments, but distal DVTs was more common in placebo-treated patients (*P*=0.006).
Fuji et al[40] Enoxaparin 20 mg SC QD vs enoxaparin 40 mg SC QD vs	2 DB, MC, PC, PG, RCTs Patients ≥20 years of age undergoing elective total hip arthroplasty or total knee arthroplasty	N=771 90 days (14 days of treatment)	Primary: VTE within 72 hours after completion or discontinuation of treatment, any bleeding Secondary: Adverse events	Primary: In patients undergoing total hip arthroplasty, the incidence of the primary efficacy endpoint was 41.9, 25.9 (*P*=0.022), 33.8 (*P*=0.188), and 20.0% (*P*=0.001) in placebo-, enoxaparin 20 mg QD-, enoxaparin 40 mg QD- and enoxaparin 20 mg BID-treated patients, respectively. There was no enoxaparin dose-response relation for the incidence of VTE (*P*=0.112). At the 90 day follow up, no additional episodes of VTE were reported. In the safety population, 4.9% who underwent total hip arthroplasty experienced at least one bleeding event. There was no significant difference between any of the treatments for the composite endpoint of any bleeding (*P*=0.051), and no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 20 mg SC BID vs placebo				between-group differences in major bleeding events were detected (*P*=0.354). The incidence of minor bleeding events in enoxaparin 40 mg QD-patients was sevenfold greater than that in the enoxaparin 20 mg QD-patients (*P*=0.033). In patients undergoing total knee arthroplasty, the incidence of the primary efficacy endpoint was 60.8, 44.9, 35.1 (*P*=0.001) and 29.8% (*P*<0.025) in the placebo-, enoxaparin 20 mg QD-, enoxaparin 40 mg QD- and enoxaparin 20 mg BID-treated patients, respectively. Treatment with enoxaparin 20 mg BID was not inferior to treatment with enoxaparin 40 mg QD based on the 95% CI of the between-group difference in the incidence of VTE. A dose-response relation was detected for treatment with placebo, enoxaparin 20 mg QD and enoxaparin 40 mg QD (*P*=0.001). In the safety population, nine percent of patients experienced a bleeding event. There was no difference in any bleeding event among the treatments (*P*=0.267). Secondary: In the safety population who underwent total hip arthroplasty the incidence of all adverse events was 98 vs 100% in placebo- and enoxaparin-treated patients (*P*=0.107). In the safety population who underwent total knee arthroplasty the incidence of all adverse events was 98.9 vs 100% in placebo- and enoxaparin-treated patients (*P*=0.377).
Eriksson et al[41] RECORD1 Rivaroxaban 10 mg QD for 35 days vs enoxaparin 40 mg SC QD in the evening for 35 days	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total hip replacement	N=4,541 70 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to 36 days; incidence of major bleeding beginning after the first dose of the study drug and up to two days after	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint (1.1 vs 3.7%; ARR, -2.6%; 95% CI, -3.7 to -1.5; *P*<0.001). There was no difference between rivaroxaban and enoxaparin for major bleeding events (0.3 vs 0.1%; *P*=0.18). Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to 1.0; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and then reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events,	Rivaroxaban significantly reduced the risk of DVT (0.8 vs 3.4%; ARR, -2.7; 95% CI, -3.7 to -1.7; *P*<0.001). Rivaroxaban and enoxaparin had similar rates of symptomatic VTE during treatment (0.3 vs 0.5%; ARR, -0.2%; 95% CI, -0.6 to 0.1; *P*=0.22) and follow-up (<0.1 vs 0.0%; ARR, -0.1%; 95% CI, -0.4 to 0.1; *P*=0.37). Both treatments had <0.1% cases of death occurring during follow-up (*P* value not reported). Rivaroxaban and enoxaparin had similar rates for any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and any on-treatment nonmajor bleeding events (5.8 vs 5.8%; *P* value not reported). The rate of hemorrhagic wound complications was also similar (1.5 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after the first dose of rivaroxaban or placebo were also similar (5.5 vs 5.0%; *P* value not reported). Rivaroxaban and enoxaparin had similar rates of any on-treatment adverse event (64.0 vs 64.7%; *P* value not reported). The incidence of death during the on-treatment period was similar between the two treatments (0.3 vs 0.3%; ARR, 0%; 95% CI, -0.4 to 0.4; *P*=1.00). Of the four deaths that occurred with rivaroxaban, two were possibly related to VTE. Of the four deaths that occurred with enoxaparin, one was related to VTE.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			death	
Kakkar et al[42] RECORD2 Rivaroxaban 10 mg QD for 31 to 39 days vs enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.	DB, DD, MC, RCT Patients ≥18 years of age undergoing complete hip replacement	N=2,509 75 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to day 30 to 42; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE, (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). Major bleeding occurred at a rate <0.1% with both rivaroxaban and enoxaparin (*P* value not reported). The one major bleeding event with enoxaparin was deemed unrelated to the treatment drug by the adjudication committee. Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban significantly reduced the risk of DVT (1.6 vs 8.2%; ARR, 6.5%; 95% CI, 4.5 to 8.5; *P*<0.0001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.2 vs 1.2%; ARR, 1.0%; 95% CI, 0.3 to 1.8; *P*=0.004); however, the rates during follow-up were similar (0.1 vs 0.2%; ARR, 0.1%; 95% CI, -0.2 to 0.4; *P*=0.62). The incidence of death during the follow-up period was similar between the two treatments (0.0 vs 0.2%; ARR, 0.2%; 95% CI, -0.1 to 0.6; *P*=0.50). Rates of any on-treatment bleeding (6.6 vs 5.5%; *P* value not reported) and any on-treatment nonmajor bleeding (6.5 vs 5.5%; *P* value not reported) were similar between the two treatments. Hemorrhagic wound complications also occurred at similar rates (1.6 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after initiation of rivaroxaban or placebo was also similar (4.7 vs 4.1%; *P* value not reported). Adverse events from any cause were similar between the two treatments (62.5 vs 65.7%; *P* values not reported). The incidence of on-treatment death was similar between the two treatments (0.2 vs 0.7%; ARR, 0.5%; 95% CI, -0.2 to 1.1; *P*=0.29).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			treatment nonmajor bleeding, hemorrhagic wound complications, any postoperative bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events, death	
Lassen et al[43] RECORD3 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin as administered 12 hour preoperatively and reinitiated six to eight hours after wound	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total knee replacement	N=2,531 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days post surgery; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (9.6 vs 18.9%; ARD, -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). The rate of major bleeding was similar between the two treatments (0.6 vs 0.5%; *P*=0.77). Secondary: Rivaroxaban significantly reduced the risk of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01). Rivaroxaban significantly reduced the risk of DVT (9.6 vs 18.2%; ARD, -8.4; 95% CI, -11.7 to -5.2; *P*<0.001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.7 vs 2.0%; ARD, -1.3%; 95% CI, -2.2 to -0.4; *P*=0.005); however, during follow-up the rates were similar (0.4 vs 0.2%; ARD, 0.2%; 95% CI, -0.3 to 0.6; *P*=0.44). The incidence of death during follow-up was similar between the two treatments

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
closure. All patients received either placebo tablets or placebo injection.			death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow up period, any on-treatment bleeding or any major bleeding occurring between intake of the first dose of the study medication and two days after the last dose, nonmajor bleeding, adverse events, death	(ARD, -0.2%; 95% CI, -0.6 to 0.2; *P*=0.21). Rates of any on-treatment bleeding (4.9 vs 4.8%; *P*=0.93) or any major bleeding between the start of treatment and two days after the last dose (0.6 vs 0.5%; *P*=0.77) were similar between the two treatments. The rate of nonmajor bleeding was also similar (4.3 vs 4.4%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (12 vs 13%; *P* value not reported). The incidence of death during treatment was similar between the two treatments (0.0 vs 0.2%; ARD, -0.2%; 95% CI, -0.8 to 0.2; *P*=0.23)
Turpie et al[44] RECORD4 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 30 mg SC BID for 10 to 14 days	DB, DD, MC, RCT Patients ≥18 years of age undergoing total knee replacement	N=3,148 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause 17 days after surgery; incidence of major bleeding beginning after the first dose of the study drug and up	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (6.9 vs 10.1%; ARD, -3.19%; 95% CI, -5.67 to -0.71; *P*=0.0118). There was no difference in the rate of major bleeding between the two treatments (0.7 vs 0.3%; *P*=0.1096). Secondary: Rivaroxaban did not reduce the risk of major VTE compared to enoxaparin (1.2 vs 2.0%; ARD, -0.80; 95% CI, -1.34 to 0.60; *P*=0.1237).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was initiated 12 to 24 hours after wound closure. All patients received either placebo tablets or placebo injection.			to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of asymptomatic DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow-up period, clinically relevant nonmajor bleeding, any on-treatment bleeding, any nonmajor bleeding, hemorrhagic wound complications, adverse events, death	The rates of asymptomatic DVT were similar between the two treatments (*P* value not reported). Rivaroxaban did not reduce the risk of symptomatic VTE on-treatment (0.7 vs 1.2%; ARD, -0.47; 95% CI, -1.16 to 0.23; *P*=0.1868) or during follow-up (0.2 vs 0.2%; ARD, 0.00%; 95% CI, -0.32 to 0.32; *P*=0.9979). The incidence of death during follow-up was similar between the two treatments (0.3 vs 0.2%; ARD, 0.06%; 95% CI, -0.35 to 0.50; *P*=0.8044). The rates of clinically relevant nonmajor bleeding (10.2 vs 9.2%; *P* value not reported) and any on-treatment bleeding (10.5 vs 9.4%; *P*=0.3287) were similar between the two treatments. The rate of hemorrhagic wound complications was also similar (1.4 vs 1.5%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (20.3 vs 19.6%; *P* value not reported). The rates of on-treatment death were similar between the two treatments (0.1 vs 0.2%; *P*=0.7449).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Colwell et al[45] Enoxaparin 30 mg SC BID vs warfarin, dose adjusted to maintain an INR between 2.0 to 3.0	MC, OL, PG, RCT Patients ≥18 years of age scheduled to undergo elective unilateral primary hip arthroplasty and had no history that would preclude anticoagulant therapy	N=3,011 3 months (14 days of treatment)	Primary: Symptomatic VTE disease, major bleeding Secondary: Not reported	Primary: During the course of the trial, 3.7% of patients had VTE disease; 3.6 vs 3.7% of enoxaparin- and warfarin-treated patients (*P* value not reported). During hospitalization (up to 14 days), 0.3 vs 1.1% of enoxaparin- and warfarin-treated patients had VTE disease (*P*=0.0083). Within the first week after discharge from the hospital, 0.7 vs 1.0% of patients had VTE disease (*P* value not reported). Between the first and second week after discharge, the corresponding rates were 1.1 vs 0.4% (*P* values not reported). Major or minor bleeding occurred in 8.7% of patients; 10.0 vs 7.4% of enoxaparin- and warfarin-treated patients. Eighteen (1.2%) and eight (0.5%) of these patients had major bleeding (*P*=0.055), and 143 (9.4%) and 106 (7.1%) had minor bleeding (*P*=0.021). Secondary: Not reported
Fitzgerald et al[46] Enoxaparin 30 mg SC BID vs warfarin, dose adjusted to maintain an INR between 2.0 to 3.0	MC, OL, PG, PRO, RCT Patients ≥38 years of age undergoing a primary unilateral total knee arthroplasty	N=349 4 to 14 days	Primary: DVT, PE, overt hemorrhage Secondary: Not reported	Primary: Treatment with enoxaparin was associated with a significantly lower incidence of VTE (25 vs 45%; *P*=0.0001). The estimated odds for the development of VTE in warfarin-treated patients were 2.52 times greater (95% CI, 2.00 to 3.19). Major hemorrhagic episodes occurred in two and five percent of warfarin- and enoxaparin-treated patients (*P*=0.17). The prevalence of major and minor hemorrhagic episodes was significantly lower in the warfarin-treated patients (23 vs 34%; *P*=0.04). Secondary: Not reported
Leclerc et al[47] Enoxaparin 30 mg SC BID vs	DB, MC, RCT Adult patients undergoing knee arthroplasty	N=670 6 months (up to 14 days of treatment)	Primary: DVT, clinically overt bleeding Secondary: Not reported	Primary: DVT was detected in 51.7 (95% CI, 44.7 to 58.5) vs 36.9% (95% CI, 30.4 to 43.9) of warfarin- and enoxaparin-treated patients, respectively. This corresponds with a RRR of 28.6% (95% CI, 11.1 to 43.1) with enoxaparin treatment (*P*=0.003). The ARD was 14.8% in favor of enoxaparin (95% CI, 5.3 to 24.1).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
warfarin, dose adjusted to maintain INR between 2.0 to 3.0				Clinically overt bleeding occurred in 26.6 (95% CI, 22.2 to 31.7) vs 30.1% (95% CI, 25.4 to 35.2; *P*>0.2) of warfarin- and enoxaparin-treated patients. Six (1.8%; 95% CI, 0.8 to 3.8) vs seven (2.1%; 95% CI, 1.0 to 4.2) warfarin- and enoxaparin-treated patients developed major hemorrhage (*P*>0.2). The ARD was 0.3% in favor of warfarin (95% CI, -2.4 to 1.8). Secondary: Not reported
No authors listed[48] The Danish Enoxaparin Study Group Enoxaparin 40 mg SC QD for 7 days vs dextran 60 mg/mL IV for 5 days	PRO, RCT Patients ≥18 years of age undergoing elective total hip replacement	N=283 7 to 11 days	Primary: DVT, bleeding Secondary: Not reported	Primary: A diagnosis of DVT occurred in a total of 31 patients; seven out of 108 and 24 out of 111 enoxaparin- and dextran-treated patients (*P*=0.0013). No patient developed clinical symptoms suggestive of PE during the trial. Minor bleeding events occurred in 14 and 26 enoxaparin- and dextran-treated patients (*P* value not significant). Secondary: Not reported
Senaran et al[49] Enoxaparin 40 mg SC QD vs heparin 5,000 units SC TID Treatment was scheduled for 7 to 10 days.	PRO, RCT Patients ≥18 years of age scheduled for hip arthroplasty with no history that would preclude anticoagulant therapy	N=100 6 weeks (7 to 10 days of treatment)	Primary: Symptomatic VTE, major bleeding Secondary: Not reported	Primary: During the course of the trial, two patients had VTE disease; all were in the heparin group. No patient had a PE. Between the first and second week after discharge, two enoxaparin-treated patients had VTE disease and were admitted back to the hospital. None of the patients died during the course of the trial or in the period of six weeks after discharge. Major or minor bleeding occurred in seven patients; eight vs six percent of heparin- and enoxaparin-treated patients. Of these patients, two and zero enoxaparin- and heparin-treated patients had a major bleed. One and all enoxaparin- and heparin-treated patients reported minor bleeding. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McLeod et al[50] Enoxaparin 40 mg SC QD vs heparin 5,000 units SC TID	DB, PRO, RCT Adult patients undergoing colorectal or rectal surgery	N=1,349 Up to 10 days	Primary: VTE, bleeding complications, thrombocytopenia Secondary: Not reported	Primary: The rate of VTE was the same for both treatments (9.4%). The total bleeding event rate was significantly lower in heparin-treated patients (6.2 vs 10.1%; *P*=0.003), primarily because of an excess of minor bleeding in enoxaparin-treated patients. The rate of major bleeding events was also nonsignificantly higher in enoxaparin-treated patients (1.5 vs 2.7; 95% CI -0.4 to 2.8; *P*=0.136). Thrombocytopenia occurred in six patients with each treatment. Secondary: Not reported
Kleber et al[51] Enoxaparin 40 mg SC QD vs UFH 5,000 units SC TID	MC, OL, PG, RCT Patients ≥18 years of age hospitalized for severe respiratory disease or heart failure and confined to bed for >2/3rds of each day	N=668 10±2 days	Primary: Thromboembolic events up to one day after the treatment period Secondary: Not reported	Primary: Thromboembolic events were confirmed in 8.4 and 10.4% in enoxaparin- and UFH-treated patients (incidence difference [UFH-enoxaparin], 2.0%; 90% CI, -2.5 to 6.5), which did not cross the one-sided equivalence region of four percent, and thus indicating with a probability of 95% that treatment with enoxaparin is at least as effective as UFH (*P*=0.015). The overall incidence of thromboembolic events was higher in patients with heart failure (12.6%) than in patients with respiratory disease (6.8%) Secondary: Not reported
De et al[52] Enoxaparin 40 mg SC QD vs UFH 5,000 units SC BID	PRO, RCT Critically ill patients >40 years of age scheduled to undergo major elective surgery who require ≥6	N=178 6 months (up to 6 days of treatment)	Primary: Mortality, VTE, safety Secondary: Not reported	Primary: Nine (11.1%) and six (eight percent) enoxaparin- and heparin-treated patients died in the postoperative period. One (1.23%) enoxaparin-treated patient developed a DVT on the seventh postoperative day (*P*=0.51) compared to two (2.66%) UFH-treated patients who developed a DVT in the sixth and tenth postoperative day (*P*=0.51). Eight (9.87%) enoxaparin-treated patients developed wound hematoma or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	days of hospitalization			gastrointestinal bleeding compared to 18 (24%) UFH-treated patients who had bleeding either from the gastrointestinal tract or from the incision or tracheostomy site, which revealed a significant increased risk for hemorrhagic complications with UFH treatment (*P*=0.01). Subgroup analysis showed no increased risk of hemorrhagic complications with respect to major events (*P*=0.48); however, there was a significantly increased risk of minor hemorrhagic events with treatment with UFH compared to enoxaparin (*P* value not reported). Secondary: Not reported
Colwell et al[53] Enoxaparin 30 mg SC BID vs enoxaparin 40 mg SC QD vs UFH 5,000 units SC TID	DB, RCT Patients ≥40 years of age who were scheduled for either primary or revision hip replacement	N=607 Up to 7 days	Primary: DVT, bleeding complications Secondary: Not reported	Primary: Overall, 10% of the 604 patients for whom clinical data were available had evidence of DVT. The rate of DVT was five, 15 and 12% of enoxaparin 30 mg- , enoxaparin 40 mg- and UFH-treated patients. The rate of DVT was significantly lower for enoxaparin 30 mg-treated patients compared to UFH- (*P*=0.014) and enoxaparin 40 mg-treated patients (*P*=0.0002). The rate was not different between enoxaparin 40 mg- and UFH-treated patients (*P*=0.24). The rates of major and minor bleeding episodes were similar among the three treatments. The overall rate of major bleeding events for all 607 patients was four percent. The rate was four, one and six percent of enoxaparin 30 mg- , enoxaparin 40 mg- and UFH-treated patients. The rate was significantly lower for enoxaparin 40 mg-treated patients compared to UFH-treated patients (*P*=0.02). Secondary: Not reported
Simonneau et al[54] Enoxaparin 40 mg SC QD vs nadroparin* 2,850 units SC QD	DB, DD, MC, PG, PRO, RCT Patients undergoing elective resection of colorectal adenocarcinoma	N=1,296 42 to 60 days (up to 7 to 11 days of treatment)	Primary: VTE up to day 12, major bleeding up to day 12 Secondary: Total, proximal and distal asymptomatic	Primary: By day 12, VTE occurred in 15.9 and 12.6% of nadroparin- and enoxaparin-treated patients (RR, 1.27; 95% CI, 0.93 to 1.74). The incidence of major bleeding was significantly lower in nadroparin-treated patients (7.3 vs 11.5%; *P*=0.012). Secondary: There was a higher incidence of distal DVT in nadroparin-treated patients (12.5

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment was scheduled to last up to 7 to 11 days.			DVT; symptomatic VTE and the composite of asymptomatic proximal DVT or symptomatic nonfatal VTE or VTE-related death up to day 12; total and symptomatic VTE up to day 60; mortality; any other bleeds; transfusion requirements; thrombocytopenia; other adverse events	vs 8.6%; RR, 1.45; 95% CI, 0.99 to 2.11). The incidence of proximal DVT was similar between the two treatments (3.2 vs 2.9%; respectively; RR, 1.12; 95% CI, 0.55 to 2.30). There were more cases of symptomatic VTE, including PE, in enoxaparin-treated patients (1.4 vs 0.2%; RR, 0.12; 95% CI, 0.01 to 0.92). There was one and zero fatal PEs in enoxaparin- and nadroparin-treated patients; therefore, the rate of the composite of asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE related death was 3.2 and 3.9% with nadroparin and enoxaparin treatment (RR, 0.82; 95% CI, 0.43 to 1.56). By day 60, the overall incidence of symptomatic VTE was 0.5 and 0.6% of nadroparin- and enoxaparin-treated patients (*P* value not reported). During the study treatment, two (0.3%) and eight (1.3%) nadroparin- and enoxaparin treated-patients died (RR, 0.24; 95% CI, 0.05 to 1.15). The incidence of any other adverse events did not differ between the two treatments.
Eriksson et al[55] Fondaparinux 2.5 mg SC QD vs placebo All patients received OL fondaparinux 2.5 mg SC QD for six to 8 days.	DB, PC, PRO, RCT Patients ≥18 years of age who were undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck if surgery was planned within 48 hours after admission	N=656 25 to 31 days (up to 6 to 8 days of treatment)	Primary: VTE, major bleeding Secondary: Total, proximal and distal DVT; symptomatic VTE, death, other bleeding, transfusion requirements, other adverse events	Primary: Fondaparinux significantly reduced the incidence of VTE compared to placebo, from 35.0 to 1.4%, with a RRR of 95.9% (95% CI, 87.2 to 99.7; *P*<0.001). The rate of treatment for a VTE event during the DB treatment period, based on the local site assessment, was 4.6 vs 22.3% in fondaparinux- and placebo-treated patients. The total outcome of major bleeding was 2.4 vs 0.6% in fondaparinux- and placebo-treated patients (*P*=0.06). Secondary: Treatment with fondaparinux significantly reduced the incidence of total, proximal and distal-only DVT (*P*<0.001 for each comparison). Treatment with fondaparinux significantly reduced the incidence of symptomatic VTE, from 2.7 to 0.3%, with a RRR of 88.8% (95% CI, 67.7 to 100; *P*=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Symptomatic PE occurred in three and zero placebo- and fondaparinux-treated patients. There were no differences in the overall incidence of adverse events and in overall mortality between the two treatments (*P* values not reported).
Agnelli et al[56] Fondaparinux 2.5 mg SC QD vs dalteparin 2,500 units once, followed by 5,000 units SC QD Treatment was scheduled to last five to nine days.	DB, DD, RCT Patients due to undergo abdominal surgery expected to last >45 minutes under general anesthesia and were >60 years of age, or >40 years of age with ≥1 additional risk factor	N=2,927 30±2 days (up to 5 to 9 days of treatment)	Primary: VTE, major bleeding Secondary: Total, proximal and distal DVT; symptomatic VTE up to day 10, symptomatic VTE up to day 30±2 days; death; other reported bleeding; thrombocytopenia; any other adverse events	Primary: The rate of VTE was 4.6 vs 6.1% in fondaparinux- and dalteparin-treated patients (RRR, 24.6%; 95% CI, -9.0 to 47.9; *P*=0.144). The corresponding OR was 0.74, with an upper 95% confidence limit of 1.09, below the predetermined criterion of 1.70 for noninferiority. The incidence of major bleeding was 3.4 and 2.4% in fondaparinux- and dalteparin-treated patients (*P*=0.122). Secondary: The incidence of any (4.2 vs 5.8%; *P*=0.10; RRR, 27.5%; 95% CI, -6.3 to 50.6), proximal (0.5 vs 0.5%; *P*=1.0; RRR, 0.1%; 95% CI, -244.70 to 70.9) and distal (3.9 vs 5.3%; *P*=0.14; RRR, 26.1%; 95% CI, -10.1 to 50.5) DVTs were similar between the two treatments. By day 10, the rate of symptomatic VTEs was the same with each treatment (0.5%). By the end of follow up (day 32), the rates of symptomatic VTE were 0.8 vs 1.0% in fondaparinux- and dalteparin-treated patients (*P* value not reported). The incidence of other adverse events was similar between the two treatments (other bleeding: 2.2 vs 1.6%; death: 1.0 vs 1.4%; *P* values not reported).
Lassen et al[57] Fondaparinux 2.5 mg SC QD vs	DB, RCT Patients ≥18 years of age scheduled for primary elective total hip	N=2,309 35 to 49 days (up to 5 to 9 days of treatment)	Primary: VTE up to day 11, major bleeding Secondary: Total, proximal and distal DVT;	Primary: By day 11, significantly fewer fondaparinux-treated patients had a VTE (4 vs 9%; treatment effect, -5.2%; 95% CI, -8.1 to -2.7; *P*<0.0001; RRR, -55.9%; 95% CI, -72.8 to -33.1). The number of patients who had major bleeding did not differ between the two treatments (*P*=0.11).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 40 mg SC QD Treatment was scheduled to last five to nine days.	replacement surgery or revision of ≥1 component of a previously implanted total hip prosthesis		symptomatic VTE up to day 11; symptomatic VTE up to day 49; death; other bleeding; transfusion requirements; thrombocytopenia; any other adverse events	Secondary: The number of total (4 vs 9%; treatment effect, -5.1%; 95% CI, -8.0 to -2.6; *P*<0.0001; RRR, -56.1%; 95% CI, -73.2 to -32.9), proximal (1 vs 2%; treatment effect, -1.8%; 95% CI, -3.7 to -0.5; *P*=0.0021; RRR, -73.8%; 95% CI, -95.2 to -24.4) and distal (3 vs 7%; treatment effect, -4.0%; 95% CI, -6.8 to -1.7; *P*<0.0001; RRR, -54.8%; 95% CI, -74.1 to -27.4) DVTs were significantly lower in fondaparinux-treated patients. The incidence of symptomatic VTE did not differ between the two treatments (*P*=0.73). Significantly fewer fondaparinux-treated patients were treated for a VTE event by day 11 on the basis of local-site assessment (four vs nine percent; *P*<0.0001). Between days one and 49, 1% of patients in each treatment group had symptomatic VTE. Incidences of other bleeding (4 vs 3%), transfusion requirements (63 vs 61%), death (0 vs 0.2%) and any other adverse events did not differ between the two treatments (*P* values not reported).
Bauer et al[58] Fondaparinux 2.5 mg SC QD vs enoxaparin 30 mg SC BID Treatment was scheduled to last five to nine days.	DB, RCT Patients ≥18 years of age and were undergoing elective major knee surgery	N=1,049 35 to 49 days (up to 5 to 9 days of treatment)	Primary: VTE up to day 11, major bleeding Secondary: Total, proximal and distal DVT up to day 11; symptomatic VTE up to day 11; symptomatic VTE up to day 49; death; other bleeding; a need for transfusion; thrombocytopenia; any other adverse	Primary: The incidence of VTE by day 11 was 27.8 vs12.5% in enoxaparin- and fondaparinux-treated patients (reduction in risk, 55.2%; 95% CI, 36.2 to 70.2; *P*<0.001). Eleven and one fondaparinux- and enoxaparin-treated patient(s) had a major bleeding event (*P*=0.006). Secondary: Treatment with fondaparinux had a significant 54.5 (*P*=0.06) and 55.9% (*P*<0.001) reduction in the risk of proximal and distal DVT. The incidence of symptomatic VTE was low and did not differ between the two treatments (0.6 vs 1.4%; *P*=0.34). By day 49, the incidence of symptomatic VTE did not differ between the treatments (1.0 vs 1.9%; *P* value not reported). The incidence of minor bleeding (2.7 vs 3.7%), a need for transfusion (42.9 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			event	38.1%), death (0.4 vs 0.6%) and other adverse events did not differ between the two treatments (*P* values not reported).
Eriksson et al[59] Fondaparinux 2.5 mg SC QD vs enoxaparin 40 mg SC QD Treatment was scheduled to last five to nine days.	DB, MC, RCT Patients ≥18 years of age scheduled to undergo standard surgery for fracture of the upper third of the femur, including the femoral head and neck	N=1,250 35 to 49 days (up to 5 to 9 days of treatment)	Primary: Rate of VTE up to day 11, major bleeding Secondary: Total, proximal or distal DVT or symptomatic VTE up to day 11, symptomatic VTE up to day 49, death, minor bleeding, need for transfusion, thrombocytopenia	Primary: The incidence of VTE by day 11 was 8.3 vs 19.1% in fondaparinux- and enoxaparin-treated patients, corresponding to a decrease of 10.8%, or a RRR of 56.4% (95% CI, 39.0 to 70.3; *P*<0.001) with fondaparinux treatment. Major bleeding occurred by day 11 in 18 out of 831 and 19 out of 842 fondaparinux- and enoxaparin-treated patients (*P*=1.00). Secondary: The incidence of total, proximal and distal-only DVT was significantly lower with fondaparinux treatment (*P*<0.001 for all three comparisons). The incidence of symptomatic VTE was low (6.5%), with no difference between the two treatments (*P* value not reported). By day 49, the incidence of symptomatic VTE was similar between the two treatments (2.0 vs 1.5%; *P* value not reported). By day 49, 4.6 vs 5.0% of fondaparinux- and enoxaparin-treated patients died (*P* value not reported). Minor bleeding occurred significantly more often with fondaparinux treatment (*P*=0.02). Transfusion requirements and the incidence of other adverse events during treatment or follow up did not differ significantly between treatments (*P* values not reported).
Turpie et al[60] Fondaparinux 2.5 mg SC QD vs	DB, MC, RCT Patients ≥18 years of age undergoing a first elective total hip replacement or a	N=2,275 35 to 49 days (up to 5 to 9 days of treatment)	Primary: Rate of VTE up to day 11, major bleeding Secondary: Total, proximal or	Primary: By day 11, the proportion of patients who developed VTEs was lower in fondaparinux-treated patients compared to enoxaparin treated patients, but the difference was not significant (6 vs 8%; *P*=0.099). The number of patients with major bleeding by day 11 did not differ between the two treatments (*P*=0.11).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 30 mg SC BID Treatment was scheduled to last five to nine days.	revision of ≥1 component of a previously implanted total hip prosthesis		distal DVT or symptomatic VTE up to day 11; symptomatic VTE up to day 49; death; minor bleeding; need for transfusion; thrombocytopenia	Secondary: By day 11, fondaparinux-treated patients had significantly fewer total (6 vs 8%; *P*=0.047) and distal (4 vs 7%; *P*=0.0.37) DVTs compared to patients receiving enoxaparin. The number of proximal DVTs did not differ between the two treatments (2 vs 1%; *P*=0.42). Few symptomatic VTEs were recorded in total, with fewer in enoxaparin-treated patients (0.1 vs 1.0%; *P*=0.0062). By day 49, fewer enoxaparin-treated patients had symptomatic VTE (1 vs 3%; difference, 1%; 95% CI, 0.05 to 3.10; *P*=0.013). The number of patients who had died by day 49 did not differ between the treatments (*P* value not reported). Other bleeding, transfusion requirements and any other adverse events arising during treatment or follow up did not differ between the two treatments (*P* values not reported).
Turpie et al[61] Fondaparinux vs enoxaparin	MA (4 DB, MC, RCT) Patients ≥18 years of age who were scheduled for primary elective total hip replacement surgery or revision of ≥1 component of a previously implanted total hip prosthesis, elective major knee surgery or standard surgery	N=7,344 35 to 49 days (1 to 9 days of treatment)	Primary: Incidence of VTE, major bleeding Secondary: Total, proximal and distal-only DVT and symptomatic VTE up to day 11; PE up to day 49	Primary: The overall incidence of VTE up to day 11 was lower in fondaparinux-treated patients compared to enoxaparin treated patients (6.8 vs 13.7%; common odds reduction, 55.2%; 95% CI, 45.8 to 63.1; *P*<0.001). In total hip replacement, hip fracture and major knee replacement surgery patients, the odds reductions for VTE up to day 11 were 45.3, 61.6 and 63.1% in favor of fondaparinux, respectively. The incidence of symptomatic VTE by day 11 was low and did not differ between the two treatments (0.6 vs 0.4%; *P*=0.25). Overall, there were 96 major bleeding events among the 3,616 fondaparinux-treated patients compared to 63 events among the 3,621 enoxaparin-treated patients (2.7 vs 1.7%; *P*=0.008) up to day 11. There were two bleeding events in a critical organ among enoxaparin-treated patients (one of which was fatal) compared to none among fondaparinux-treated patients. Twelve bleeding episodes leading to another operation were reported among fondaparinux-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	for fracture of the upper third of the femur, including femoral head and neck			patients compared to eight episodes among enoxaparin-treated patients. Of the 3,616 fondaparinux-treated patients, 2.3% experienced overt bleeding associated with a bleeding index of two or more compared to 1.5% of the 3,621 enoxaparin-treated patients. Thus the difference in major bleeding was mainly accounted for by an excess of bleeding with a bleeding index of two or more. Secondary: Compared to enoxaparin, the incidence of total, distal and proximal DVT up to day 11 was lower in fondaparinux-treated patients. The common odds reduction in favor of fondaparinux for proximal DVT up to day 11 was 57.4% (95% CI, 35.6 to 72.3). Fatal PE occurred in 0.1% of fondaparinux- and enoxaparin-treated patients, respectively. Corresponding numbers with respect to nonfatal PE were 0.2% for both treatments. Between days one and 49, the incidence of fatal PE was 0.3 vs 0.3%, and for nonfatal PE, 0.5 vs 0.4% in fondaparinux- and enoxaparin-treated patients, respectively.
Eikelboom et al[62] Fondaparinux 2.5 mg QD vs LMWH (dalteparin, enoxaparin) or placebo	MA (8 Phase III RCTs) Patients receiving treatment for the prevention of VTE	N=13,085 30 days	Primary: Death within 30 days Secondary: Not reported	Primary: At 30 days, the risk of death was seven fold higher among patients with a major bleeding event (8.6 vs 1.7%; adjusted HR, 6.69; 95% CI, 4.60 to 10.51). There was a consistent pattern of reduced mortality in fondaparinux-treated patients irrespective of whether patients experienced major bleeding (6.8 vs 11.4%; adjusted HR, 0.58; 95% CI, 0.27 to 1.23) or no major bleeding (1.5 vs 1.9%; HR, 0.77; 95% CI, 0.59 to 1.02). Patients who developed major bleeding were older, were more likely to be male, had a lower body weight and lower creatinine clearance and were more likely to receive treatment with fondaparinux. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oran et al[63] LMWH (dalteparin, enoxaparin, nadroparin*, reviparin*, tinzaparin*)	MA (7 trials) Patients with prosthetic heart valves who received LMWH as an anticoagulant during their pregnancy	N=75 (81 pregnancies) Duration varied	Primary: Thromboembolic complications, major bleeding, death, frequency of abortion, frequency of stillbirth, congenital abnormalities, neonatal hemorrhage Secondary: Not reported	Primary: Thromboembolic complications were reported in 10 out of 81 pregnancies (12.35%; 95% CI, 5.19 to 19.51); seven valve thromboses, two thrombotic cerebrovascular accidents and one embolism. There were no thromboembolic events in patients with prosthetic aortic valves. All of the patients who had thromboembolic complications were receiving LMWH throughout pregnancy. In nine of these 10 pregnancies, the patients were on a fixed dose of LMWH instead of adjusting the dose to maintain a therapeutic anti-Xa level. Seven of these nine patients were on standard therapeutic doses for the particular preparation they were using, while two patients were on a low, prophylactic dose. Only one of the 10 patients with thromboembolic complications was on LMWH with an aim to keep the anti-Xa level in therapeutic range. One of the 81 pregnancies was reported to be complicated with peripartum hemorrhage; anti-Xa levels were not monitored. There was no mortality reported during LMWH treatment, but a patient died three months postpartum after discharge from the hospital secondary to intracranial hemorrhage. Of the 81 pregnancies, spontaneous abortion occurred in six (7.40%; 95% CI, 1.70 to 13.10) and stillbirth in one (1.23%; 95% CI, 0.01 to 2.45). One patient had a termination of pregnancy during the first trimester because of medical risks associated with pregnancy. Two other women had fetal losses in the second trimester; one because of hydrocephalus while she was on warfarin, and the other after ovarian surgery while she was on IV heparin. The rate of live births was 87.65% (95% CI, 80.49 to 94.81). Secondary: Not reported
van Dongen et al[64] LMWH QD vs	SR (5 RCTs) Patients with VTE receiving initial treatment	N=1,508 Duration varied	Primary: Symptomatic recurrent VTE, major hemorrhagic	Primary: Three of the five trials reported on the recurrence of symptomatic VTE. Pooled analysis revealed no difference in the incidence of recurrent thromboembolic events between the two treatments (OR, 0.82; 95% CI, 0.49 to 1.39).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LMWH BID			episodes during initial treatment or within 48 hours after treatment cessation Secondary: Extension of the thrombus size, overall mortality, incidence of the post-thrombotic syndrome	All trials reported on the occurrence of major hemorrhage events. Pooled analysis revealed a nonsignificant lower incidence in hemorrhagic events in LMWH QD-treated patients (OR, 0.77; 95% CI, 0.40 to 1.45). Secondary: Data on change in thrombus size could be extracted from two trials. A combined OR was calculated and demonstrated no difference between the two treatments (OR, 1.41; 95% CI, 0.66 to 3.01). Four trials reported data on overall mortality. Pooled analysis showed that there was a nonsignificant difference in mortality in favor of treatment with LMWH BID-treated patients (OR, 1.14; 95% CI, 0.62 to 2.08). None of the trials reported data on post-thrombotic syndrome.
Testroote et al[65] LMWH vs no treatment or placebo	SR (6 RCTs) Adult patients with lower leg immobilization in an ambulant setting	N=1,490 Duration varied	Primary: Morbidity Secondary: Mortality, adverse outcomes of treatment	Primary: *All patients* The incidence of thromboembolic events in the control group ranged from 4.3 to 40.0% and from 0 to 37.0%. *Only patients with below knee casts* In five trials, the incidence of DVT in LMWH-treated and control-treated patients ranged from 0 to 37.0% and from 3.6 to 40.0% (OR, 0.54; 95% CI, 0.37 to 0.80). *PE* In the trials, PE was a rare complication in immobilization of the lower extremity. In one trial, four symptomatic control-treated patients had a PE and in another one patient in the group without prophylaxis had clinical signs of a PE, but a diagnosis was not confirmed. *Only patients with conservative treatment* In four trials, the incidence ranged from zero to 11.8% and from 4.3 to 17.3% of LMWH- and control-treated patients (OR, 0.35; 95% CI, 0.19 to 0.62). *Only surgically treated patients* In four trials, the incidence of DVT ranged from 7.2 to 37.0% and from 18.0 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				40.0% of LMWH- and control-treated patients (OR, 0.54; 95% CI, 0.37 to 0.80). *Fractures or soft tissue injuries* Five trials provided information on patients with fractures and the results were significant in favor treatment with LMWH (OR, 0.53; 95% CI, 0.36 to 0.78). When analyzing the results from patients with soft tissue injuries, there is a significant difference as well (OR, 0.39; 95% CI, 0.22 to 0.68). *Distal or proximal DVT* In five trials, the incidence of distal segment DVT ranged from 0 to 34.7% and from 2.5 to 34.0% in LMWH- and control-treated patients (OR, 0.61; 95% CI, 0.42 to 0.89). Proximal DVT was rare; there were eight events in a total of 614 LMWH-treated patients (incidences ranging from 0 to 4.0%) vs 20 out of 603 control-treated patients (incidences ranging from 0.9 to 6.4%) (OR, 0.41; 95% CI, 0.19 to 0.91). *Patients with symptomatic VTE* In all but one trial, symptomatic VTE was observed in 0.3 vs 2.5% of LMWH- and control-treated patients (OR, 0.16; 95% CI, 0.05 to 0.56). Secondary: No mortality was reported in the six included trials. Major side effects (hematoma, acute bleeding, allergy and thrombocytopenia) were rare. Major bleeding did occur in two of 750 patients. There were no significant differences between the treatments.
van der Heijden et al[66] VKAs vs LMWH	SR (7 RCTs) Patients with symptomatic DVT receiving long-term treatment	N=1,137 3 to 9 months	Primary: Recurrent symptomatic VTE, major bleeding complications, mortality Secondary: Not reported	Primary: All seven trials reported the occurrence of recurrent symptomatic VTE during the first three to six months after randomization. Six trials showed no differences between treatment with LMWH and VKAs, and one trial found a significant OR of 0.38 (95% CI, 0.17 to 0.86) in favor of treatment with LMWH. When the seven trials are combined, the rate of recurrent symptomatic VTE was 6.7 vs 4.8% in VKA- and LMWH-treated patients, corresponding to a nonsignificant reduction in favor of LMWH (OR, 0.70; 95% CI, 0.42 to 1.16).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Six trials evaluated the occurrence of recurrent symptomatic VTE during a period of six to nine months after cessation of the allocated treatment. The rate of recurrent symptomatic VTE was 3.5 vs 5.0% of VKA- and LMWH-treated patients, corresponding to nonsignificant difference in favor of VKA treatment (OR, 1.46; 95% CI, 0.80 to 2.69). All seven trials reported the incidence of major bleeding during allocated treatment, with six trials finding no difference between the two treatments and one finding a significant difference in favor of treatment with LMWH (OR, 0.12; 95% CI, 0.02 to 0.89). When the trials were combined, 2.5 vs 0.9% VKA- and LMWH-treated patients had a major bleed; a significant difference in favor of treatment with LMWH (OR, 0.38; 95% CI, 0.15 to 0.94). No major bleeding occurred in the additional nine months of follow-up. All seven trials reported on mortality during the allocated treatment, with the individual trials not finding a significant difference between the two treatments. In the combined analysis, 2.5 vs 3.7% of VKA- and LMWH-treated patients died (OR, 1.51; 95% CI, 0.77 to 2.97). Six trials extended the follow-up period for an additional six to nine months and found that the rate of death was 3.5 vs 3.9% (OR, 1.11; 95% CI, 0.58 to 2.15). Secondary: Not reported
Salazar et al[67] DTI (dabigatran†, desirudin, ximelagatran*) vs warfarin or LMWH (dalteparin, enoxaparin)	SR (12 RCTs) Patients who have undergone total hip replacement or total knee replacement	N=21,642 (efficacy) N=27,360 (safety) Duration varied	Primary: Mortality associated with VTE, incidence of proximal VTE, mortality associated with treatment, appearance of serious hepatopathy, appearance of	Primary and Secondary end points are reported together in the groupings below. *Major, total and symptomatic VTE* Combined analysis from two trials comparing DTIs to LMWH demonstrated that when evaluating the combination of both surgery groups, no difference was observed between the two treatments (557 out of 10,736 vs 392 out of 6,692 events/patients; OR, 0.91; 95% CI, 0.69 to 1.19). Evaluation of the individual surgery groups had similar results. No difference was observed between the two treatments for total VTE (data not reported) or symptomatic VTE (234 out of 12,056 vs 143 out of 7,563; OR, 1.04; 95% CI, 0.84 to 1.29). Combined analysis from three trials comparing ximelagatran to warfarin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			other serious adverse effects associated with treatment Secondary: Incidence of distal VTE, presence of hepatopathy after treatment, morbidity associated with treatment	demonstrated no statistical difference between the two treatments (95 out of 2,498 vs 83 out of 1,829 events/patients; OR, 0.85; 95% CI, 0.63 to 1.15). There were fewer total VTE events in DTI-treated patients (555 out of 2,514 vs 543 out of 1,840; OR, 0.68; 95% CI, 0.59 to 0.78). No difference between the two treatments were observed for symptomatic VTE (47 out of 3,022 vs 48 out of 2,237; OR, 0.80; 95% CI, 0.53 to 1.21). *Major/significant and total bleeding events* Combined analysis from eleven trials comparing DTIs to LMWH demonstrated a nonsignificant higher number of major significant bleeding events in DTI-treated patients (334 out of 13,753 vs 138 out of 8,356 events/patients; OR, 1.17; 95% CI, 0.87 to 1.58). In the comparison of each independent dose, only dabigatran 225 mg BID showed more bleeding events in the DTI group (OR, 1.90; 95% CI, 1.05 to 3.44) in the combination of both surgeries and specifically in total hip replacement (26 out of 270 vs 13 out of 270; OR, 2.11; 95% CI, 1.06 to 4.19). Combined analysis from ten trials demonstrated no difference between the two treatments in terms of total bleeding events; however, more events were observed in DTI-treated patients undergoing total hip replacement (2,370 out of 5,949 vs 1,374 out of 4,378; OR, 1.40; 95% CI, 1.06 to 1.85). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated more major/significant bleeding events with ximelagatran, but the difference was not statistically significant (30 out of 3,022 vs 13 out of 2,237 events/patients; OR, 1.76; 95% CI, 0.91 to 3.38). Partial and total bleeding events were very similar to major bleeding events. *All-cause mortality* Combined analysis of eleven trials comparing DTIs to LWMH demonstrated a nonsignificant higher all-cause mortality event rate with DTI treatment (15 out of 13,730 vs four out of 8,335 events/patients; OR, 1.72; 95% CI, 0.68 to 4.35). When including follow-up events the difference met statistical significance (41 out of 13,730 vs 11 out of 8,335; OR, 2.06; 95% CI, 1.10 to 3.87). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (six out of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				3,013 vs four out of 2,230 events/patients; OR, 1.19; 95% CI, 0.36 to 4.01), even when follow-up events were included (10 out of 3,013 vs five out of 2,230; OR, 1.62; 95% CI, 0.57 to 4.58). *ALT greater than three times the upper normal limit* The seven trials comparing DTIs to LMWH had high heterogeneity; therefore, results could not be combined. Fewer events were observed in DTI-treated patients, but with high heterogeneity, in the ximelagatran trials. No difference was noted when treatment with dabigatran was compared to treatment with LMWH, but these trials had very high heterogeneity. Combined analysis of two trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (18 out of 2,493 vs 21 out of 1,768 events/patients; OR, 0.52; 95% CI, 0.27 to 0.97), even when follow-up events were included (11 out of 2,484 vs one out of 1,783; OR, 5.61; 95% CI, 1.00 to 31.64). *Volume of blood loss* No difference was observed between treatment with DTIs and LMWH in the combined analysis of five trials (n=8,782; WMD, 5.12; 95% CI, -33.81 to 44.04), but these trials had high heterogeneity. No difference was observed between ximelagatran and warfarin in the combined analysis of three trials (n=5,259; WMD, -7.12; 95% CI, -17.08 to 2.84), with no heterogeneity. *Time effect of the beginning of anticoagulation* Trials comparing DTIs to LMWH that began anticoagulation before surgery demonstrated fewer major (OR, 0.54; 95% CI, 0.35 to 0.83) and total (OR, 0.72; 95% CI, 0.63 to 0.82) VTE in DTI-treated patients in both surgery groups. There was also no difference regarding symptomatic VTE. Trials that began anticoagulation after surgery demonstrated more major (OR, 1.68; 95%, 1.12 to 2.52) and total (OR, 1.29; 95% CI, 0.69 to 2.39) VTE events in DTI-treated patients in both surgery groups. Again, there was no difference regarding symptomatic VTE.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Trials that began anticoagulation before surgery demonstrated a non- significant greater incidence of major (OR, 1.64; 95% CI, 0.85 to 3.15) and total (OR, 1.45; 95% CI, 0.93 to 2.28) bleeding events in DTI-treated patients in both combined surgeries and in the individual analysis of each surgery. There was no significant difference regarding mortality. *Extended prophylactic anticoagulation vs standard prophylactic anticoagulation* No difference was found in major or total VTE between DTI- and LMWH-treated patients. Symptomatic VTE events in extended anticoagulation occurred more with dabigatran in comparison to LMWH, but the difference was not statistically significant (25 out of 2,293 vs five out of 1,142 events/patients; OR, 2.51; 95% CI, 0.96 to 5.67). In standard anticoagulation, no difference between DTI- and LMWH-treated patients was noted (76 out of 3,351 vs 37 out of 1,542; OR, 0.99; 95% CI, 0.67 to 1.48). Regarding safety, no difference in major or total bleeding events was noted. All-cause mortality, transaminase levels and blood loss were not evaluated.
Erkens et al[68] LMWH vs UFH	SR (23 RCTs) Patients with VTE	N=9,587 6 months (5 to 14 days of treatment)	Primary: Incidence of symptomatic recurrent VTE Secondary: Change in thrombus size based on pre and post treatment venograms, frequency of major hemorrhagic episodes during initial treatment or	Primary: The occurrence of symptomatic VTE was evaluated during the initial treatment period, at three months and at six months follow-up. Additionally, combining all trials with long term follow up gave a comparison of recurrent thromboembolism at the end of follow up. Pooled analysis demonstrates a significant reduction in recurrent VTE with LMWH treatment during the initial treatment period (OR, 0.68; 95% CI, 0.48 to 0.97), at three and six months follow up (OR, 0.71; 95% CI, 0.56 to 0.90 and OR, 0.68; 95% CI, 0.48 to 0.96, respectively) and at the end of follow up (OR, 0.70; 95% CI, 0.57 to 0.85). During the initial treatment, 1.7 vs 2.4% of LMWH- and UFH-treated patients had the recurrence of symptomatic VTE. After follow up of three months, the period in most of the trials for which oral anticoagulant therapy was given, 3.6 vs 5.2% of enoxaparin- and UFH-treated patients had a recurrent VTE (*P* value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			within 48 hours after treatment cessations, overall mortality at the end of follow up	Venograms were obtained before and after heparin treatment in 12 trials, which demonstrated a reduction of thrombus size in 53 and 44% of LMWH- and UFH-treated patients; treatment with LMWH was associated with a better venographic outcome (OR, 0.69; 95% CI, 0.59 to 0.81). Of the individual LMWH preparations, a significant better venographic outcome was observed with nadroparin* (OR, 0.54; 95% CI, 0.37 to 0.79), reviparin* (OR, 0.59; 95% CI, 0.43 to 0.80) and ardeparin* (OR, 0.37; 95% CI, 0.14 to 0.99) treatment. Twenty of the included trials evaluated the occurrence of major hemorrhage during the initial treatment, which demonstrated a significant reduction in major hemorrhagic complications in favor of treatment with LMWH (OR, 0.58; 95% CI, 0.40 to 0.83). Of the individual trials, only one trial using tinzaparin treatment demonstrated a significant reduction in major hemorrhage (OR, 0.19; 95% CI, 0.06 to 0.59), whereas two using enoxaparin and reviparin treatment showed a nonsignificant increase in major hemorrhage favoring UFH treatment (OR, 1.70; 95% CI, 0.42 to 6.87 and OR, 1.26; 95% CI, 0.49 to 3.19, respectively). At the end of initial treatment, 1.1 vs 1.9% of LMWH- and UFH-treated patients had a major hemorrhage (*P* value not reported). Nineteen trials evaluated the overall mortality at the end of follow up, which demonstrated the rate of mortality was significantly lower in LMWH-treated patients (OR, 0.77; 95% CI, 0.63 to 0.93). In LMWH-treated patients, 4.4% died compared to 5.8% of UFH-treated patients.
Othieno et al[69] LMWH vs UFH (in-patient use only) The patients were either randomized to home or in-patient treatment.	SR (6 RCTs) Patients with proven VTE in whom there is no contraindication to heparin therapy and whose home circumstances were adequate	N=1,708 Duration varied	Primary: The incidence and outcome of complications of VTE or its treatment (PE, recurrent DVT, venous gangrene, heparin complications, death), patient satisfaction,	Primary: The trials demonstrated that patients treated at home with LMWH are less likely to have recurrence of VTE compared to hospital treatment with UFH or LMWH (fixed effect RR, 0.61; 95% CI, 0.42 to 0.90). Home-treated patients had lower mortality (RR, 0.72; 95% CI, 0.45 to 1.15) and fewer major bleeding (RR, 0.67; 95% CI, 0.33 to 1.36), but were more likely to have minor bleeding than those in the hospital (RR, 1.29; 95% CI, 0.94 to 1.78), though these were not significant. In one of the trials, quality of life questionnaires were completed by over 80% of both trial groups before randomization, at the end of the treatment course and at

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			cost/incidence of treatment complications Secondary: Not reported	12 and 24 weeks. Two out of the six criteria (physical activity and social functioning) demonstrated a significant advantage in LMWH-treated patients at the completion of initial treatment but not before or after. The results of one trial were used for comparison of the cost of treatment calculations between the two arms of the trial. There was a 64% saving in LMWH-treated patients as opposed to UFH-treated patients, largely due to lower hospital costs. The authors stated this was a conservative estimate of the potential reductions in cost. Secondary: Not reported
Kanaan et al[70] LMWH/fondaparinux vs UFH	MA (9 RCTs) Medically ill patients with risk factors for VTE who had been followed for up to 7 to 21 days	N=12,391 Duration varied	Primary: VTE, DVT, fatal or nonfatal PE, major or minor bleeding, fatal bleeding, VTE-related death Secondary: Not reported	Primary: LMWH/fondaparinux was shown to significantly reduce VTE when compared to placebo (OR, 0.59; 95% CI, 0.47 to 0.74; *P*<0.001) with an ARR of 1.68% and an NNT of 60, and when compared to UFH or placebo (OR, 0.64; 95% CI, 0.52 to 0.79; *P*<0.001); the ARR was 1.15% and the NNT was 87. No difference between LMWH and UFH was found in reducing the incidence of VTE (OR, 0.89; 95% CI, 0.54 to 1.46). DVT events were significantly reduced with LMWH/fondaparinux compared to placebo (OR, 0.60; 95% CI, 0.47 to 0.75; *P*≤0.001) and this treatment was associated with an ARR of 1.36% and a NNT of 74. This reduction was driven by dalteparin evaluations; the remaining four LMWH/fondaparinux trials did not find an association with reduced events compared to placebo at seven to 21 days. No significant difference was found in the incidence of DVT when comparing LMWH/fondaparinux to UFH alone (OR, 0.92; 95% CI, 0.56 to 1.52), suggesting LMWH/fondaparinux and UFH are similar in reducing DVT events in medically ill patients. When LMWH/fondaparinux was compared to the combination of UFH or placebo, a significant reduction of DVT events was observed (OR, 0.64; 95% CI, 0.51 to 0.79; *P*≤0.001), and these data were associated with an ARR of 2.1% and an NNT of 48. A reduction in PE events was not found when LMWH/fondaparinux was compared to placebo (OR, 0.54; 95% CI, 0.28 to 1.05). This finding remained

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				consistent when LMWH/fondaparinux was compared to UFH (OR, 0.80; 95% CI, 0.22 to 2.9) and to UFH or placebo (OR, 0.59; 95% CI, 0.34 to 1.03). LMWH/fondaparinux was associated with a significantly increased risk for minor bleed compared to placebo (OR, 1.64; 95% CI, 1.18 to 2.29; *P*=0.003), with an ARI of 2.24% and a NNH of 45. Of note; this increased risk was driven by one evaluation of enoxaparin. There was no difference in the incidence of minor bleeding between LMWH/fondaparinux and UFH (OR, 0.68; 95% CI, 0.27 to 1.70) or between LMWH/fondaparinux and UFH or placebo (OR, 1.30; 95% CI, 0.86 to 1.97). Major bleeding events were similar among all comparisons: LMWH/fondaparinux vs placebo (OR, 1.65; 95% CI, 0.80 to 3.40); LMWH/fondaparinux vs UFH (OR, 0.69; 95% CI, 0.29 to 1.68); LMWH/fondaparinux vs UFH or placebo (OR, 1.16; 95% CI, 0.66 to 2.04). When minor and major bleeding events were combined, a significant increase in the incidence of any bleeding was shown when comparing LMWH/fondaparinux to placebo (OR, 1.69; 95% CI, 1.24 to 2.27; *P*≤0.001). The increased risk was driven mainly by a trial of dalteparin and enoxaparin. No significant difference was observed when comparing LMWH/fondaparinux to UFH (OR, 0.72; 95% CI, 0.44 to 1.18) or LMWH/fondaparinux to UFH or placebo (OR, 1.25; 95% CI, 0.87 to 1.80). The composite end point of any bleeding or death from VTE was also significantly increased when comparing LMWH/fondaparinux to placebo (OR, 1.35; 95% CI, 1.07 to 1.70; *P*=0.01), with an ARI of 1.73% and an NNH of 58, which was driven by an increase in minor bleeding. This difference was not observed when comparing LMWH/fondaparinux to UFH (OR, 0.73; 95% CI, 0.48 to 1.32), or LMWH/fondaparinux to UFH or placebo (OR, 1.15; 95% CI, 0.88 to 1.50). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Handoll et al[71] Injectable anticoagulants (LMWH, UFH) vs physical agents (compression stockings, arteriovenous foot pumps) vs placebo or no treatment Treatment modalities were also compared to each other.	SR (31 RCTs) Patients undergoing surgery for proximal femoral fracture	N=2,958 Duration not reported	Primary: DVT, PE, death within the study treatment period or up to six months of hip fracture surgery, complications associated with therapy, development of postphlebitic limb, length of hospital stay Secondary: Not reported	Primary: *Any heparin vs control/placebo* Out of 15 trials, there was a significant reduction in incidence of any DVT when heparin was compared to either placebo or control (26 vs 42%; RR, 0.60; 95% CI, 0.50 to 0.71). Out of 12 trials, there was no difference observed in the incidence of any PE between the treatments. Mortality was mentioned in nine trials and was increased, but not significantly, in heparin-treated patients when compared to control or placebo treated patients (12 vs 10%; RR, 1.16; 95% CI, 0.77 to 1.74). Overall, the quality of reporting of potential adverse effects was poor. Complications, primarily related to bleeding, were reported in 11 trials. There was one case of postphlebitic limb in a LMWH-treated patient compared to none among control-treated patients. Incomplete data were given in one trial that reported the duration of hospitalization was comparable in the two groups, and another trial made no comment on the slight increase in the mean days in hospital in the control group (32.9 vs 35.7 days). *Mechanical methods vs control* The primary outcome in all five trials was DVT. In two trials, the incidence of any DVT was significantly reduced (7 vs 22%; RR, 0.31; 95% CI, 0.19 to 0.51) when the use of a physical device was compared to no application. From all five trials, the numbers of any PE significantly reduced in patients assigned to physical devices (2.1 vs 6.4%; RR, 0.40; 95% CI, 0.17 to 0.96). Fatal PE was potentially, but not significantly, reduced by the use of physical devices (RR, 0.27; 95% CI, 0.07 to 1.08). All trials mentioned mortality but results were unavailable for one. Mortality was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				potentially, but no significantly, reduced by the use of physical devices (RR, 0.50; 95% CI, 0.22 to 1.14). Complications associated with interventions included the development of blisters, unacceptability of the foot pump and non-compliance perhaps due to discomfort. One trial found no significant difference between the two treatments in the incidence of hematoma, hematuria and stroke. There was also no significant difference in the volume of blood transfused; all patients received blood transfusions. One trial reported two cases of postphlebitic limb. Though the data given by the two trials reporting hospital stay showed a slight reduction in hospital stay for the intervention group, these were insufficient to enable tests for significance. *LMWH vs UFH* Five trials directly compared LMWH to UFH and the comparison showed a significant reduction in the incidence of any DVT (19 vs 28%; RR, 0.67; 95% CI, 0.48 to 0.94) for LMWH-treated patients. Pooled analysis demonstrated that the nonsignificant excess in any PE in LMWH-treated patients (3.7 vs 0.6%; RR, 3.29; 95% CI, 0.82 to 13.32) resulted mainly from one trial. Pooled analysis from three trials demonstrated no difference in mortality (5 vs 6%; RR, 0.95; 95% CI, 0.31 to 2.36) between the two treatments. Complications, including bleeding and wound complications were reported in four trials. Only hematoma data from two trials could be pooled, but the nonsignificant result should be viewed in the context of the low numbers involved (3 vs 5%). *Any heparin vs mechanical methods* One trial compared treatment with LMWH to intermittent pneumatic compression

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in 36 patients; there were no differences between the two treatments in any DVT, fatal PE, mortality, bleeding complications and transfusions. Another trial compared treatment with LMWH to intermittent pneumatic compression up to 48 hours post operatively followed by LMWH and provided results for 45 patients. There were no differences between the two treatments in any DVT, nonfatal PE or number receiving transfusions. *Miscellaneous comparisons* One trial compared treatment with LMWH 20 mg BID to 40 mg BID and there was no difference in the incidence of any, proximal or distal DVT. No PE or deaths were reported. Two hematomas occurred in each group. One trial compared treatment with UFH adjusted to fixed dose and revealed no difference in any, proximal or distal DVT. Two trials compared treatment with LMWH started preoperatively to postoperatively and revealed a significant reduction in any DVT preoperatively-treated patients. No PE was found in one trial. Pooled mortality data showed no difference between the two treatments. One trial reported no difference in bleeding or transfusion requirements. No difference was also found between the two treatments for either wound hematoma or infection. One trial compared dalteparin to enoxaparin and showed no significant difference between the two treatments in the incidence of any or proximal DVT. No PE was detected in the trial period. By two months, two deaths occurred in enoxaparin-treated patients; both were considered to be due to thromboembolic causes. No differences between the two treatments were reported for intra- or post-operative blood losses, transfusion volumes or bleeding complications. Secondary: Not reported
Rasmussen et al[72] LMWH	SR (4 RCTs) Patients	N=901 Duration	Primary: Incidence of DVT, PE or fatal PE	Primary: No trials evaluating prolonged treatment with UFH, oral anticoagulants or mechanical methods were identified.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs UFH vs mechanical methods vs VKAs (acenocoumarol* or phenprocoumon*) vs placebo or no treatment	undergoing general abdominal or pelvic surgery for cancer or benign disease receiving prolonged thrombo-prophylaxis interventions with in-hospital prophylaxis and later placebo or no treatment	varied	within 30 days after surgery, postoperative three month mortality rate Secondary: Symptomatic VTE, bleeding complications, mortality	*LMWH vs placebo or no treatment* The incidence of VTE after major abdominal or pelvic surgery was 14.3 (95% CI, 11.2 to 17.8) vs 6.1% (95% CI, 4.0 to 8.7) in the control group and in out-of-hospital LMWH-treated patients (OR, 0.41; 95% CI, 0.26 to 0.63; *P*<0.0001). The NNT to avoid one case of VTE was 13 (95% CI, 9 to 24). Prophylaxis with LMWH as compared to control also offered better protection against all DVT (OR, 0.43; 95% CI, 0.27 to 0.66; NNT, 14; 95% CI, 9 to 27) and proximal DVT (OR, 0.27; 95% CI, 0.13 to 0.57; NNT, 26; 95% CI, 17 to 59). Secondary: *LMWH vs placebo or no treatment* Prolonged thromboprophylaxis with LMWH was associated with a significant reduction of symptomatic VTE (OR, 0.22; 95% CI, 0.06 to 0.80; *P*=0.02; NNT, 66; 95% CI, 36 to 400). There was no difference regarding the incidence of overall (both major and minor) bleeding between the treatments (3.7%; 95% CI, 2.4 to 5.5 vs 4.1%; 95% CI, 2.7 to 6.0; OR, 1.11; 95% CI, 0.62 to 1.97; *P*=0.73; NNH, 250; 95% CI, 200 to 333). There was no difference in mortality between the two treatments (5.80%; 95% CI, 3.9 to 8.3 vs 5.35%; 95% CI, 3.6 to 7.6; OR, 1.12; 95% CI, 0.65 to 1.93; *P*=0.68; NNH, 250; 95% CI, 142 to 333).
Brookenthal et al[73] Thromboprophylaxis (aspirin, dextran, heparin [with or without antithrombin III], LMWH [ardeparin*, enoxaparin, tinzaparin*], lower extremity pneumatic compression stockings, or warfarin)	MA (14 trials) Patients receiving prophylaxis for ≥7 days for an elective total knee arthroplasty	N=3,482 Duration varied	Primary: Total DVT, proximal DVT, distal DVT, symptomatic PE, fatal PE, minor bleeding, major bleeding, total bleeding, intracranial hemorrhage, non-PE mortality, all-	Primary: For total DVT, all treatments, except dextran and aspirin, protected significantly better than placebo (*P*<0.0001). For proximal DVT, no comparison against placebo was available, and rates ranged from 1.7 (aspirin) to 12.8% (SC heparin/antithrombin III). The only significant difference was between treatment with LMWH and warfarin (5.9 vs 10.2%; *P*=0.0002). There was a strong trend that aspirin protected better than warfarin (1.7 vs 10.2%; *P*=0.0106). For distal DVT, no comparison against placebo was available. LMWH (24.4%) protected significantly better than dextran (71.1%; *P*=0.0001), warfarin (35.6%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo A prophylactic agent of interest was compared to another method of interest or placebo.			cause mortality Secondary: Not reported	*P*=0.0001) and aspirin (55.2%; *P*=0.0001). Warfarin (35.6%) protected significantly better than aspirin (55.2%; *P*=0.0045) but worse than SC heparin (21.5%; *P*=0.0029). Aspirin (55.2%) protected significantly less than SC heparin (21.5%; *P*=0.0001) and pneumatic compression stockings (29.5%; *P*=0.0051). Rates of symptomatic PE ranged from 0.0 (aspirin, pneumatic compression stockings and placebo) to 0.4% (warfarin, SC heparin); there was no significant detectable difference among the agents. No fatal PE occurred with any treatment. The rate of total bleeding ranged from 8.6 (aspirin) to 18.9% (SC heparin). No comparison with placebo was available. The rate of minor bleeding ranged from 8.6 (aspirin) to 18.3% (SC heparin). Rates of major bleeding ranged from 0.0 (aspirin, pneumatic compression stockings) to 2.4% (LWMH), but no difference between treatments were noted. There were no observed intracranial hemorrhages. Rates for overall and non-PE mortality ranged from 0.0 (aspirin, SC heparin, pneumatic compression stockings, placebo, SC heparin/antithrombin III and dextran) to 0.3% (warfarin), but no difference among the treatments were noted. Secondary: Not reported
Safety				
Uchino et al[74] Dabigatran vs control (warfarin,	MA (7 RCTs; 2 trials of stroke prophylaxis in AF, 1 trial in acute VTE, 1 in ACS, and 3 of short term	N=30,514 Duration not specified	Primary: Acute coronary events (MI or ACS) Secondary: Overall mortality	Primary: Dabigatran was significantly associated with a higher risk of MI or ACS compared to control (237/20,000 [1.19%] vs 83/10,514 [0.79%]; OR, 1.33; 95% CI, 1.03 to 1.71; *P*=0.03). The risk of MI or ACS was similar when using revised RE-LY trial results (OR, 1.27; 95% CI, 1.00 to 1.61; *P*=0.05) or after exclusion of short term trials (OR, 1.33; 95% CI, 1.03 to 1.72; *P*=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin, or placebo)	prophylaxis in DVT) Patient population not specified			No relationship between the baseline risk of acute coronary events and the OR for acute coronary events associated with dabigatran use (*P*=0.61). Secondary: Six trials reported on overall mortality. Dabigatran was significantly associated with lower mortality compared to control (945/19,555 [4.83%] vs 524/10,444 [5.02%]; OR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.04).

*Not available within the United States.
†Not Food and Drug Administration approved for this indication.
Drug regimen abbreviations: BID=twice-daily, IV=intravenous, QD=once-daily, SC=subcutaneous, TID=three times daily
Clinical trial abbreviations: ARD=absolute risk difference, ARI=absolute risk increase, ARR=absolute risk reduction, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, SB=single-blind, SD=standard deviation, SR=systematic review
Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, DTI=direct thrombin inhibitor, DVT=deep vein thrombosis, HIT=heparin induced thrombocytopenia, INR=International Normalized Ratio, LMWH=low molecular weight heparin, MI=myocardial infarction, NSTE ACS=non-ST-segment elevation acute coronary syndrome, NYHA=New York Heart Association, PE=pulmonary embolism, STEMI=ST-segment elevation myocardial infarction, UFH=unfractionated heparin, VKA=vitamin K antagonist, VTE=venous thromboembolism

Special Populations

Table 5. Special Populations[1-3,75-76]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dalteparin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances <30 mL/minute, monitor anti-Xa levels to determine the appropriate dose.	No dosage adjustment required.	B	Yes (minimal; % not reported); use with caution.
Enoxaparin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment for moderate renal dysfunction is required. Renal dose adjustment is required for severe renal dysfunction (creatinine clearances <30 mL/minute).*	Not studied in hepatic dysfunction; use with caution.	B	Unknown; use with caution.
Fondaparinux	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Use caution in patients with a creatinine clearance 30 to 50 mL/minute. Contraindicated in patients with a creatinine clearance <30 mL/minute.	No dosage adjustment required.	B	Unknown; use with caution.

*Please see Table 10 for the renal dosing of enoxaparin.

Adverse Drug Events

Table 6. Adverse Drug Events[1-3]

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux
Bleeding Reactions			
Anorectal bleeding	-	-	-
Any bleeding reaction	4.4 to 13.6	-	-
Cerebral/intracranial bleeding	-	-	-

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux
Epistaxis	-	-	1.3
Hemarthrosis	-	-	-
Hematemesis	-	-	-
Hematoma	-	-	2.1 to 2.8
Hematuria	2.9	<1 to 2	-
Hemopericardium	-	-	-
Hemoptysis	-	-	-
Hemorrhage	-	5 to 13	-
Injection site bleeding	-	-	-
Injection site hematoma	0.2 to 7.1	3 to 5	-
Major bleeding	0.4 to 5.6	0 to 4	1.2 to 3.4
Melena	-	-	-
Minor bleeding	-	-	2.2 to 3.1
Ocular bleeding	-	-	-
Other clinically overt bleeding	-	-	1
Postoperative hemorrhage	-	-	0.6 to 2.4
Postoperative transfusions	5.7 to 15.9	-	-
Purpura	-	-	0 to 3.5
Rectal bleeding	-	-	-
Reoperation due to bleeding	0.5 to 1.3	-	-
Retroperitoneal/intra-abdominal bleeding	-	-	-
Surgical site non-fatal major bleeding	-	-	2.7
Vaginal hemorrhage	-	-	-
Wound hematoma	0.4 to 3.9	-	-
Other			
Abscess	-	-	-
Agranulocytosis	-	-	-
Allergic reactions	✔	-	-
Anemia	-	<1 to 16	1.5 to 19.6
Angina pectoris	-	-	-
Back pain	-	-	-
Bullous eruption	-	-	0 to 3.1
Cellulitis	-	-	-
Cardiac arrhythmia	-	-	-
Chest pain	-	-	-
Cholestatic hepatitis	-	-	-
Confusion	-	2.2	1.2 to 3.1
Constipation	-	-	-
Diarrhea	-	2.2	-
Dizziness	-	0.6 to 3.6	-
Dyspepsia	-	-	-
Dyspnea	-	3.3	-
Dysuria	-	-	-
Ecchymosis	-	<1	-
Edema	-	2	-
Elevations in serum transaminases	✔	5.9 to 6.1	0.7 to 2.6
Epidermal necrolysis	-	-	-
Fever	-	5 to 8	-
Flatulence	-	-	-
Gastrointestinal disorder	-	-	-

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux
Granulocytopenia	-	-	-
Headache	-	-	-
Healing impaired	-	-	-
Hypersensitivity	-	-	-
Hypertension	-	-	-
Hypokalemia	-	-	0.0 to 4.2
Hypotension	-	-	0.3 to 3.5
Infection	-	-	-
Insomnia	-	-	0.9 to 5.0
Ischemic necrosis	-	-	-
Local reactions	2 to 13	2	✔
Myocardial infarction/coronary thrombosis	-	-	-
Nausea	-	2.5 to 3.0	-
Neoplasm	-	-	-
Pain	-	-	-
Pancytopenia	-	-	-
Peripheral edema	-	<1	-
Peripheral ischemia	-	-	-
Pneumonia	-	-	-
Postoperative wound infection	-	-	4.9
Priapism	-	-	-
Pruritus	-	-	-
Pulmonary embolism	-	-	-
Rash	-	-	-
Respiratory disorder	-	-	-
Skin disorder	-	-	-
Stevens-Johnson syndrome	-	-	-
Tachycardia	-	-	-
Thrombocythemia	-	-	-
Thrombocytopenia	✔	2.8	✔
Thromboembolism	-	-	-
Thrombophlebitis	-	-	-
Urinary retention	-	-	-
Urinary tract infection	-	-	-
Urticaria	-	-	-
Vomiting	-	-	-
Wound drainage increase	-	-	0.6 to 4.5

-Event not reported or incidence <1%.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[1-3]

Contraindication	Dalteparin	Enoxaparin	Fondaparinux
Bacterial endocarditis	-	-	✔
Body weight <50 kg (venous thromboembolism prophylaxis only)	-	-	✔
History of heparin induced thrombocytopenia or heparin induced thrombocytopenia with thrombosis	✔	-	-
Hypersensitivity; individual agent, heparin (enoxaparin), pork (enoxaparin) or benzyl alcohol	✔	✔	-

Contraindication	Dalteparin	Enoxaparin	Fondaparinux
(enoxaparin)			
In patients undergoing epidural/neuraxial anesthesia as a treatment for unstable angina and non-Q-wave myocardial infarction or for prolonged venous thromboembolism prophylaxis	✔	-	-
Major active bleeding	✔	✔	✔
Severe renal impairment	-	-	✔
Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of the agent	-	✔	✔

Black Box Warning for Fragmin® (dalteparin), Lovenox® (enoxaparin)[1,2,76]

WARNING
Spinal/Epidural hematomas: Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include use of indwelling epidural catheters; concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs, platelet inhibitors or other anticoagulants; a history of traumatic or repeated epidural or spinal punctures or a history of spinal deformity or spinal injury. Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Black Box Warning for Arixtra® (fondaparinux)[3,76]

WARNING
Spinal/Epidural hematomas: When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids or fondaparinux for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma that can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis, such as nonsteroidal anti-inflammatory drugs, platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. Frequently monitor patients for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the potential benefit vs risk before neuraxial intervention in patients anticoagulated or scheduled to be anticoagulated for thromboprophylaxis. Use fondaparinux injection, like other anticoagulants, with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders; active ulcerative and angiodysplastic gastrointestinal disease; hemorrhagic stroke; or shortly after brain, spinal or ophthalmological surgery or in patients treated concomitantly with platelet inhibitors.

Warnings and Precautions

Table 8. Warnings and Precautions[1-3]

Warning/Precaution	Dalteparin	Enoxaparin	Fondaparinux
Benzoyl alcohol; each multi-dose vial contains benzoyl alcohol as a preservative	✔	✔	-
Increased risk of bleeding in patients who weigh <50 kg compared to patients with higher weights	-	-	✔

Warning/Precaution	Dalteparin	Enoxaparin	Fondaparinux
Increased risk of bleeding in patients with impaired renal function due to reduced clearance	-	-	✔
Increased risk of hemorrhage; use with caution in conditions with increased risk of hemorrhage	✔	✔	✔
Interchangeability with other heparins; agent cannot be used interchangeably with heparin or other low molecular weight heparins	-	✔	-
Neuraxial anesthesia and post-operative indwelling epidural catheter use; spinal or epidural hematomas, which may result in long term or permanent paralysis, can occur with concomitant use of anticoagulants	-	-	✔
Percutaneous coronary revascularization procedures; to minimize the risk of bleeding adhere precisely to the intervals recommended between doses	-	✔	-
Thrombocytopenia can occur	✔	✔	✔
Use of agent for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied	-	✔	-
Use with care in patients with congenital or acquired bleeding disorders; active ulcerative and angiodysplastic gastrointestinal disease; hemorrhagic stroke; uncontrolled arterial hypertension; diabetic neuropathy; or shortly after brain, spinal, or ophthalmological surgery	-	-	✔
Use with care in the following conditions; patients with bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic neuropathy, renal dysfunction, and hemorrhage	-	✔	-
Use with extreme caution in patients with a history of heparin-induced thrombocytopenia	-	✔	-

Drug Interactions

Whenever possible, medications that may enhance the risk of hemorrhage should be discontinued prior to initiation of therapy with any of the injectable anticoagulants, unless these medications are essential.[1-3]

In clinical trials, concurrent use of fondaparinux with oral anticoagulants, platelet inhibitors, nonsteroidal anti-inflammatory drugs, and digoxin did not significantly affect the pharmacokinetics/pharmacodynamics of any of the medications.[3]

Table 9. Drug Interactions[1-3,76]

Generic Name	Interacting Medication or Disease	Potential Result
Low molecular heparin (dalteparin, enoxaparin)	Nonsteroidal anti-inflammatory drugs	Risk of hemorrhagic adverse reactions may be increased.

Dosage and Administration

Dalteparin is administered via subcutaneous injection, and should not be administered via intramuscular injection. Routine coagulation tests such as Prothrombin Time and Activated Partial Thromboplastin Time are relatively insensitive measures of dalteparin activity; therefore, these measurements are unsuitable for monitoring the anticoagulant effect of dalteparin. In addition, in patients receiving dalteparin who

experience platelet counts between 50,000 and 100,000/mm^3, the daily dose should be reduced by 2,500 international units until the platelet count recovers to ≥100,000/mm^3. In patients receiving dalteparin who experience platelet counts <50,000/mm^3, discontinue treatment until the platelet count returns to >50,000/mm^3.[1]

Enoxaparin can be administered via subcutaneous injection or intravenously, and should not be administered via intramuscular injection. All patients should be evaluated for a bleeding disorder before receiving enoxaparin, unless the medication is needed urgently. Coagulation parameters are also unsuitable for monitoring enoxaparin activity; therefore, routine monitoring of coagulation parameters is not required.[2]

Fondaparinux is to be administered via subcutaneous injection only.[3]

Table 10. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dalteparin	Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer: Injection: initial, 200 IU/kg SC QD for 30 days; maintenance, approximately 150 IU/kg SC QD during months two through six; maximum, daily doses should not exceed 18,000 IU Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 120 IU/kg, but not more than 10,000 IU, SC every 12 hours; maintenance, continue treatment until the patient is clinically stabilized (usual duration, five to eight days) Prophylaxis of DVT in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness: Injection: 5,000 IU SC QD* Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: preoperatively, 2,500 IU SC QD one to two hours prior to surgery; postoperatively, 2,500 IU SC QD (usual duration, five to 10 days) In patients undergoing abdominal surgery with a high risk of thromboembolic complications, the recommended dose of dalteparin is 5,000 IU SC the evening before the surgery, then 5,000 IU SC QD postoperatively (usual duration, five to 10 days); alternatively, patients with malignancy can administer 2,500 IU SC one to two hours prior to surgery, followed by 2,500 IU SC 12 hours later, then 5,000 IU SC QD (usual duration, five to 10 days)	Safety and efficacy in children have not been established.	Injection: 2,500 IU/0.2 mL‡ 5,000 IU/0.2 mL‡ 7,500 IU/0.3 mL‡ 10,000 IU/0.4 mL‡ 10,000 IU/1 mL§ 12,500 IU/0.5 mL‡ 15,000 IU/0.6 mL‡ 18,000 IU/0.72 mL‡ 95,000 IU/3.8 mL‖ 95,000 IU.9.5 mL‖

Generic Name	Adult Dose	Pediatric Dose	Availability
	Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: preoperatively, 5,000 IU SC 10 to 14 hours before surgery or 2,500 IU SC within two hours before surgery; postoperatively, 2,500 to 5,000 IU SC four to eight hours after surgery plus 5,000 IU SC QD (usual duration, five to 10 days after surgery)†		
Enoxaparin	Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 1 mg/kg SC every 12 hours for a minimum of two days and continued until clinical stabilization (usual duration, two to eight days)¶ Injection (patients with creatinine clearance <30 mL/minute): 1 mg/kg SC QD Prophylaxis of DVT in medical patients who are at risk of thromboembolic complications due to severely restricted mobility during acute illness: Injection: 40 mg SC QD (usual duration, six to 11 days)# Injection (patients with creatinine clearance <30 mL/minute): 30 mg SC QD Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: preoperatively, 40 mg SC two hours prior to surgery; postoperatively, 40 mg SC QD (usual duration, seven to 10 days)** Injection (patients with creatinine clearance <30 mL/minute): 30 mg SC QD Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: initial, 30 mg SC 12 to 24 hours after surgery or 40 mg SC QD administered 12(±3) hours prior to surgery; maintenance, 40 mg SC QD for three weeks (usual duration, seven to 10 days)# Injection (patients with creatinine clearance <30 mL/minute): 30 mg SC QD Prophylaxis of DVT in patients undergoing knee replacement surgery: Injection: initial, 30 mg SC 12 to 24 after surgery (usual duration, seven to 10 days)#	Safety and efficacy in children have not been established.	Injection (100 mg/mL): 30 mg/0.3 mL‡ 40 mg/0.4 mL‡ 60 mg/0.6 mL§ 80 mg/0.8 mL§ 100 mg/1 mL§ 300 mg/3 mL‡‡ Injection (150 mg/mL): 120 mg/0.8 mL§ 150 mg/1 mL§

Generic Name	Adult Dose	Pediatric Dose	Availability
	Injection (patients with creatinine clearance <30 mL/minute): 30 mg SC QD Treatment of acute DVT: Injection (outpatient): 1 mg/kg SC every 12 hours for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)†† Injection (outpatients with creatinine clearance <30 mL/minute): 1 mg/kg SC QD Injection (inpatient): 1 mg/kg SC BID or 1.5 mg/kg SC QD both for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)†† Injection (in patients with creatinine clearance <30 mL/minute): 1 mg/kg SC QD Treatment of acute ST-segment elevation MI: Injection: initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC BID; maximum, 100 mg for the first two doses, followed by 1 mg/kg dosing for the remaining doses Injection (patients <75 years of age with creatinine clearances <30 mL/minute): initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC QD Injection (patients ≥75 years of age with creatinine clearances <30 mL/minute): 1 mg/kg SC QD		
Fondaparinux	Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: 2.5 mg SC QD after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)§§ Prophylaxis of DVT in patients undergoing hip fracture surgery: Injection: 2.5 mg SC QD after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)‖ ‖; an extended prophylaxis course of up to 24 additional days is recommended¶¶	Safety and efficacy in children have not been established.	Injection: 2.5 mg/0.5 mL‡ 5 mg/0.4 mL‡ 7.5 mg/0.6 mL‡ 10 mg/0.8 mL‡

Generic Name	Adult Dose	Pediatric Dose	Availability
	Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: 2.5 mg SC QD after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)‖ ‖ Prophylaxis of DVT in patients undergoing knee replacement surgery: Injection: 2.5 mg SC QD after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)‖ ‖ Treatment of acute DVT: Injection: 5 (<50 kg), 7.5 (50 to 100 kg) or 10 (>100 kg) mg SC QD for ≥5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)## Treatment of acute PE: Injection: 5 (<50 kg), 7.5 (50 to 100 kg) or 10 (>100 kg) mg SC QD for ≥5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)##		

BID=twice-daily, DVT=deep vein thrombosis, IU=international units, IV=intravenous, MI=myocardial infarction, PE=pulmonary embolism, QD=once-daily, SC=subcutaneous, UA=unstable angina, VTE=venous thromboembolism
*In clinical trials, the usual duration of administration is five to 10 days.
†Up to 14 days of treatment have been well tolerated in clinical trials.
‡Available as a single-dose prefilled syringe.
§Available as a single-dose graduated prefilled syringe.
‖Available as a multiple-dose vial. After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to two weeks.
¶Up to 12.5 days of treatment have been administered in clinical trials.
#Up to 14 days of treatment have been administered in clinical trials.
**Up to 12 days of treatment have been administered in clinical trials.
††Up to 17 days of treatment have been administered in clinical trials.
‡‡Available as a multiple-dose vial.
§§Up to 10 days of treatment have been administered in clinical trials.
‖‖Up to 11 days of treatment have been administered in clinical trials.
¶¶A total of 32 days (perioperative and extended prophylaxis) was administered in clinical trials.
##Up to 26 days of treatment have been administered in clinical trials.

Clinical Guidelines

Current guidelines are summarized in Table 11. Please note that guidelines addressing thromboprophylaxis are presented globally, addressing the role of various medication classes. Due to the complexity of treatment regimens for unstable angina, acute coronary syndromes, and myocardial infarction, the associated clinical guideline summaries focus specifically on the role of the injectable anticoagulants in disease management.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic**	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international

Clinical Guideline	Recommendations
Therapy and Prevention of Thrombosis, 9th edition (2012)[8]	normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is suggested against. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • It is suggested that healthcare providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • It is suggested that concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics be avoided in patients receiving VKA therapy. • It is suggested that concomitant use of platelet inhibitors be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, it is suggested that VKA therapy be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done so abruptly rather than gradual tapering of the dose to discontinuation. • For initiation of intravenous (IV) UFH, it is suggested that initial bolus and rate of continuous infusion be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, it is suggested that dosing be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, it is suggested that the treatment dose of fondaparinux be increased from 7.5 to 10 mg/day SC.

Clinical Guideline	Recommendations
	• For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is suggested against. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is suggested against. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is suggested rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home:

Clinical Guideline	Recommendations
	routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis.

Clinical Guideline	Recommendations
	• Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjust-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjust-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as

Clinical Guideline	Recommendations
	thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours.

Clinical Guideline	Recommendations
	• Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy.

Clinical Guideline	Recommendations
	• In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or

Clinical Guideline	Recommendations
	PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran or rivaroxaban for long-term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over

Clinical Guideline	Recommendations
	no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation.
The American Heart Association: **Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association (2011)**[9]	Recommendations for initial anticoagulation for acute PE • Therapeutic anticoagulation with SC LMWH, IV or SC UFH with monitoring, unmonitored weight-based SC UFH, or SC fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation. • Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation. Fibrinolysis is not recommended for undifferentiated cardiac arrest. Recommendations for initial anticoagulation for patients with iliofemoral DVT • In the absence of suspected or proven heparin induced thrombocytopenia, patients with iliofemoral DVT should receive therapeutic anticoagulation with IV UFH, SC UFH, a LMWH agent, or fondaparinux. • Patients with iliofemoral DVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor. Recommendations for long-term anticoagulation therapy for patients with iliofemoral DVT • Adult patients with iliofemoral DVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of five days and until the INR is >2.0 for at least 24 hours, and then targeted to an INR of 2.0 to 3.0. • Patients with first episode iliofemoral DVT related to a major reversible risk factor should have anticoagulation stopped after three months. • Patients with recurrent or unprovoked iliofemoral DVT should have at least six months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation. • Cancer patients with iliofemoral DVT should receive LMWH monotherapy for at least three to six months, or as long as the cancer or its treatment (e.g., chemotherapy) is ongoing. • In children with DVT, the use of LMWH monotherapy may be reasonable.
National Institute for Health and Clinical Excellence: **Venous Thromboembolism: Reducing the Risk (Reducing the Risk of Venous Thromboembolism [Deep Vein Thrombosis and Pulmonary Embolism]**	Assessing the risks of VTE and bleeding • Assess all patients on admission to identify those who are at increased risk of VTE. Patients at high risk have had or are expected to have significantly reduced mobility for three or more days, or are expected to have ongoing reduced mobility relative to their normal state and have one or more of the following risk factors: active cancer or cancer treatment, age >60 years, critical care admission, dehydration, known thrombophilias, obesity, one or more significant comorbidities, personal history of first degree relative with a history of VTE, use of hormone replacement therapy, use of estrogen-containing contraceptive therapy, or varicose veins with phlebitis. • Regard surgical patients and patients with trauma as being at increased

Clinical Guideline	Recommendations
in Patients Admitted to the Hospital) (2010)[10]	risk of VTE if they meet one of the following criteria: surgical procedure with a total anesthetic and surgical time >90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb; acute surgical admission with inflammatory or intra-abdominal condition; expected significant reduction in mobility; or one or more of the risk factors listed above. • Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis. Prophylaxis should not be offered to patients with any of the following risk factors for bleeding, unless the risk of VTE outweighs the risk of bleeding: active bleeding, acquired bleeding disorders, concurrent use of anticoagulants known to increase the risk of bleeding, lumbar puncture/epidural/spinal anesthesia expected within the next 12 hours, lumbar puncture/epidural/spinal anesthesia within the previous four hours, acute stroke, thrombocytopenia, uncontrolled systolic hypertension, or untreated inherited bleeding disorders. • Reassess patients' risks of bleeding and VTE within 24 hours of admission and whenever the clinical situation changes. <u>Reducing the risk of VTE</u> • Do not allow patients to become dehydrated unless clinically indicated. • Encourage patients to mobilize as soon as possible. • Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE. • Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE and for whom mechanical and pharmacological VTE prophylaxis are contraindicated. <u>Reducing the risk of VTE-general medical patients</u> • Offer pharmacological VTE prophylaxis with fondaparinux, LMWH, or UFH to patients assessed to be at an increased risk of VTE. Start as soon as possible after risk assessment has been completed and continue until the patient is not an increased risk of VTE. <u>Reducing the risk of VTE-patients with stroke</u> • Anti-embolism stockings should not be offered. • Consider offering prophylactic-dose LMWH (or UFH for patients with renal failure) if a diagnosis of hemorrhagic stroke has been excluded, the risk of bleeding is assessed to be low, and the patient has one or more of the following: major restriction of mobility, previous history of VTE, dehydration, or comorbidities. Continue until the acute event is over and the patient's condition is stable. • Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device. <u>Reducing the risk of VTE-patients with cancer</u> • Offer pharmacological VTE prophylaxis with fondaparinux, LMWH, or UFH to patients who are assessed to be at an increased risk of VTE. Start as soon as possible after risk assessment is complete and continue until the patient is no longer at increased risk of VTE. • Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant. <u>Reducing the risk of VTE-patients with central venous catheters</u>

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	• Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients who are ambulant; consider prophylaxis in patients who are at an increased risk. Reducing the risk of VTE-patients in palliative care • Consider offering pharmacological VTE prophylaxis with fondaparinux, LMWH, or UFH to patients who have potentially reversible acute pathology. • Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end of life care pathway. Reducing the risk of VTE-surgical patients • For cardiac surgery, add pharmacological VTE prophylaxis with LMWH or UFH to mechanical prophylaxis in patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgment. Continue until the patient no longer has significantly reduced mobility (generally five to seven days). • For gastrointestinal, gynecological, thoracic, or urological surgeries, add pharmacological VTE prophylaxis with fondaparinux (bariatric and gastrointestinal surgery only), LWMH, or UFH to mechanical prophylaxis in patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgment. Continue until the patient no longer has significantly reduced mobility (generally five to seven days). • Extend pharmacological VTE prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis. • Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations or acute traumatic or nontraumatic hemorrhage, until the lesion has been secured or the condition is stable. • For elective hip replacement surgery, offer combined VTE prophylaxis with mechanical and pharmacological methods. Unless contraindicated, start pharmacological VTE prophylaxis after surgery with any of the following: dabigatran, fondaparinux, LMWH, rivaroxaban, or UFH. Continue for 28 to 35 days, according to the summary of product characteristics for the individual agent being used. • For elective knee replacement surgery, offer combined VTE prophylaxis with mechanical and pharmacological methods. Unless contraindicated, start pharmacological VTE prophylaxis after surgery with any of the following: dabigatran, fondaparinux, LMWH, rivaroxaban, or UFH. Continue for 10 to 14 days, according to the summary of product characteristics for the individual agent being used. • For hip fracture surgery, offer combined VTE prophylaxis with mechanical and pharmacological methods. Unless contraindicated, add pharmacological VTE prophylaxis with any of the following: fondaparinux, LMWH, or UFH. Continue for 28 to 35 days, according to the summary of product characteristics for the individual agent being used. • For other orthopedic surgeries, consider offering combined VTE prophylaxis with mechanical and pharmacological methods. Start pharmacological VTE prophylaxis six to 12 hours after surgery with any

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	of the following: LMWH or UFH. Continue until the patient no longer has significantly reduced mobility. • For vascular surgeries, offer VTE prophylaxis to patients who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE. Add pharmacological VTE prophylaxis to mechanical prophylaxis for patients who have a low risk of major bleeding with any of the following: LMWH or UFH. Continue until the patient no longer has significantly reduced mobility (generally five to seven days). • For day surgeries, offer VTE prophylaxis to patients who are assessed to be at increased risk of VTE. Add pharmacological VTE prophylaxis to mechanical prophylaxis for patients who have a low risk of major bleeding with any of the following: fondaparinux, LMWH, and UFH. If significantly reduced mobility is expected after discharge, continue for five to seven days, generally. • For other surgical patients, offer VTE prophylaxis to patients who are assessed to be at increased risk of VTE. Add pharmacological prophylaxis to mechanical prophylaxis for patients who have a low risk of major bleeding with any of the following: LMWH or UFH. Continue until the patient no longer has significantly reduced mobility, generally five to seven days. <u>Reducing the risk of VTE-other patient groups</u> • For major trauma or spinal injury, offer combined VTE prophylaxis with mechanical and pharmacological methods. If the benefits of reducing the risk of VTE outweigh the risks of bleeding and bleeding risk has been established as low, add pharmacological VTE prophylaxis to mechanical prophylaxis with any of the following: LMWH or UFH. Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility. • For lower limb plaster casts, consider offering pharmacological VTE prophylaxis after evaluating the risks and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal. • For pregnancy and up to six weeks post partum, consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) if the patient has one or more of the following risk factors: expected to have significantly reduced mobility for three or more days, active cancer or cancer treatment, age >35 years, critical care admission, dehydration, excess blood loss or blood transfusion, known thrombophilias, obesity, or one or more significant medical comorbidities: personal history of first degree relative with a history of VTE, pregnancy-related risk factor, or varicose veins with phlebitis. • For critical care patients, assess for the risks of VTE and bleeding. Offer pharmacological VTE prophylaxis if the risk of VTE outweighs the risk of bleeding.
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial**	<u>Antiplatelet therapy to support primary percutaneous coronary intervention for ST-elevation myocardial infarction</u> • Aspirin 162 to 325 mg should be given before primary percutaneous coronary intervention. • After percutaneous coronary intervention, aspirin should be continued indefinitely. • A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as

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Infarction (2013)[11]	possible or at time of primary percutaneous coronary intervention to patients with ST-elevation myocardial infarction. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg. • $P2Y_{12}$ inhibitor therapy should be given for one year to patients with ST-elevation myocardial infarction who receive a stent (bare-metal or drug-eluting) during primary percutaneous coronary intervention using clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily. • It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary percutaneous coronary intervention. • It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary percutaneous coronary intervention (with or without stenting or clopidogrel pre-treatment) in selected patients with ST-elevation myocardial infarction who are receiving UFH. • It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with ST-elevation myocardial infarction for whom primary percutaneous coronary intervention is intended. • It may be reasonable to administer intracoronary abciximab to patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. • Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support primary percutaneous coronary intervention</u> • For patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH. • In patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. • Fondaparinux should not be used as the sole anticoagulant to support primary percutaneous coronary intervention because of the risk of catheter thrombosis. <u>Adjunctive antiplatelet therapy with fibrinolysis</u> • Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with ST-elevation myocardial infarction who receive fibrinolytic therapy. • Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with ST-elevation myocardial infarction who receive fibrinolytic therapy. • It is reasonable to use aspirin 81 mg per day in preference to higher

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	maintenance doses after fibrinolytic therapy. Adjunctive anticoagulant therapy with fibrinolysis • Patients with ST-elevation myocardial infarction undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed. • Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization. Antiplatelet therapy to support percutaneous coronary intervention after fibrinolytic therapy • After percutaneous coronary intervention, aspirin should be continued indefinitely. • Clopidogrel should be provided as a 300 mg loading dose given before or at the time of percutaneous coronary intervention to patients who did not receive a previous loading dose and who are undergoing percutaneous coronary intervention within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of percutaneous coronary intervention to patients who did not receive a previous loading dose and who are undergoing percutaneous coronary intervention more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after percutaneous coronary intervention. • After percutaneous coronary intervention, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. • Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent. • Prasugrel, in a 10 mg daily maintenance dose, is reasonable after percutaneous coronary intervention. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. Anticoagulant therapy to support percutaneous coronary intervention after fibrinolytic therapy • For patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa

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	receptor antagonists have been administered. • For patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.
American College of Cardiology Foundation/American Heart Association: **2012 Focused Update Incorporated Into the 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (2012)**[12]	<u>Recommendations for antiplatelet/anticoagulant therapy in patients for whom diagnosis of unstable angina/ non-ST-elevation myocardial infarction is likely or definite-anticoagulant therapy</u> • Anticoagulant therapy should be added to antiplatelet therapy as soon as possible after presentation. • For patients in whom an invasive strategy is selected, regimens with established efficacy include enoxaparin, UFH, bivalirudin, and fondaparinux. • For patients in whom a conservative strategy is selected, regimens using enoxaparin, UFH, or fondaparinux have established efficacy. In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. o Enoxaparin or fondaparinux are preferred over UFH, unless coronary artery bypass grafting surgery is planned within 24 hours. <u>Additional considerations:</u> • For patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, heart failure, or serious arrhythmias), a stress test should be performed. • If, after stress testing, the patient is classified as being at low risk, the instructions noted below should be followed in preparation for discharge: o Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy. • For patients in whom coronary artery bypass grafting is selected as a post-angiography management strategy, anticoagulation therapy should be managed as follows: o Discontinue enoxaparin 12 to 24 hours before coronary artery bypass grafting and dose with UFH per institutional practice. o Discontinue fondaparinux 24 hours before coronary artery bypass grafting and dose with UFH per institutional practice. • For patients in whom percutaneous coronary intervention has been selected as a post-angiography management strategy, anticoagulant therapy should be discontinued after percutaneous coronary intervention for uncomplicated cases. • For patients in whom medical therapy is selected as a post-angiography management strategy and in whom no significant obstructive coronary artery disease on angiography was found, anticoagulation therapy should be administered at the discretion of the clinician. If coronary artery disease was found, anticoagulation therapy should be managed as follows: o Continue enoxaparin or fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic

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	angiography. • Patients in whom medical therapy is selected as a management strategy and in whom coronary artery disease was found on angiography should: o Continue UFH for at least 48 hours or until discharge if given before diagnostic angiography, continue enoxaparin or fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic angiography. • Patients in whom a conservative strategy is selected and who do not undergo angiography should Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2011)**[13]	Recommendations for anticoagulants • Anticoagulation is recommended for all patients in addition to antiplatelet therapy. • The anticoagulation should be selected according to both ischemic and bleeding risks and according to the efficacy/safety profile for the chosen agent. • Fondaparinux (2.5 SC daily) is recommended as having the most favorable efficacy/safety profile with respect to anticoagulation. • Enoxaparin (1 mg/kg twice-daily) is recommended when fondaparinux is not available. • If fondaparinux or enoxaparin are not available, UFH or other LMWH agents are indicated. • Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GP IIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding. • In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge. • Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated. • Crossover of heparins (UFH and LMWH) is not recommended.
American College of Cardiology Foundation/American Heart Association and American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2009 Focused Update of the 2007 Focused Update and the 2004 Guidelines for the Management of Patients with ST-Segment Elevation Myocardial Infarction and Guidelines on**	Recommendations for the use of parenteral anticoagulants (2009 focused update) • For patients undergoing percutaneous coronary intervention after having received an anticoagulant regimen, the following dosing recommendation should be followed: o For prior treatment with enoxaparin, if the last SC dose was administered at least eight to 12 hours earlier, an IV dose of 0.3 mg/kg of enoxaparin should be given. o For prior treatment with enoxaparin, if the last SC dose was administered within the prior eight hours, no additional enoxaparin should be given. o For prior treatment with fondaparinux, administer additional IV treatment with an anticoagulant possessing anti-IIa activity, taking into account whether GP IIb/IIIa receptor antagonists have been administered. Initial recognition and management in the emergency department-LMWH as ancillary therapy to reperfusion therapy • LMWH might be considered an acceptable alternative to UFH as ancillary therapy for patients <75 years of age who are receiving

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Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update) (2009)[14,15]	fibrinolytic therapy, provided that significant renal dysfunction is not present. Enoxaparin used in combination with full dose tenecteplase is the most comprehensively studied regimen in this patient population. • LMWH should not be used as an alternative to UFH as ancillary therapy in patients >75 years of age who are receiving fibrinolytic therapy. <u>Risk stratification during early hospital course-antithrombotics:</u> • IV UFH or LMWH should be used in patients after ST-segment elevation myocardial infarction who are at high risk for systemic emboli (e.g., large or anterior myocardial infarction, atrial fibrillation, previous embolus, known left ventricular thrombus, cardiogenic shock). • It's reasonable that ST-segment elevation myocardial infarction patients not undergoing reperfusion therapy who do not have a contraindication to anticoagulation be treated with IV or SC UFH or with SC LMWH for at least 48 hours. In patients whose clinical condition necessitates prolonged bed rest and/or minimized activities, it is reasonable that treatment be continued until the patient is ambulatory. o Prophylaxis for DVT with SC LMWH or with SC UFH may be useful, but the effectiveness of such a strategy is not well established in the contemporary era of routine aspirin use and early mobilization. <u>Other complications</u> • ST-segment elevation myocardial infarction patients with or without acute ischemic stroke who have a cardiac source of embolism (e.g., atrial fibrillation, mural thrombus, akinetic segment) should receive moderate intensity warfarin therapy (in addition to aspirin). The duration of warfarin therapy should be dictated by clinical circumstances. The patient should receive LMWH or UFH until adequately anticoagulated with warfarin. • DVT or PE after ST-elevation myocardial infarction should be treated with full dose LMWH for a minimum of five days and until the patient is adequately anticoagulated with warfarin. Start warfarin concurrently with LMWH and titrate to an INR of 2.0 to 3.0. • Patients with congestive heart failure after ST-elevation myocardial infarction who are hospitalized for prolonged periods, unable to ambulate, or considered at high risk for DVT and are not otherwise anticoagulated should receive low dose heparin prophylaxis, preferably with LMWH.
American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2011 Guideline for Percutaneous Coronary Intervention (2011)**[77]	<u>Interventional pharmacotherapy-anticoagulant therapy</u> • An anticoagulant should be administered to patients undergoing percutaneous coronary intervention. • Administration of IV UFH is useful in patients undergoing percutaneous coronary intervention. • An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of percutaneous coronary intervention to patients who have received fewer than two therapeutic SC doses or received the last SC enoxaparin dose eight to 12 hours before percutaneous coronary intervention. • Performance of percutaneous coronary intervention with enoxaparin may be reasonable in patients either treated with upstream SC enoxaparin for unstable angina/non ST-segment elevation myocardial

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	infarction or who have not received prior antithrombin therapy and are administered IV enoxaparin at the time of percutaneous coronary intervention. • UFH should not be given to patients already receiving therapeutic SC enoxaparin. • For patients undergoing percutaneous coronary intervention, bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. • For patients with heparin-induced thrombocytopenia, it is recommended that bivalirudin or argatroban be used to replace UFH. • Fondaparinux should not be used as the sole anticoagulant to support percutaneous coronary intervention. An additional anticoagulant with anti-IIa activity should be administered because of the risk of catheter thrombosis.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2011)**[78]	Recommendations for patients with cardioembolic stroke types • Atrial fibrillation: o For patients with ischemic stroke or transient ischemic attack with paroxysmal or permanent atrial fibrillation, anticoagulation with a VKA (target INR, 2.0 to 3.0) is recommended. o For patients unable to take oral anticoagulants, aspirin alone is recommended. o The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin. o For patients with atrial fibrillation at high risk for stroke who require temporary interruption of oral anticoagulation, bridging therapy with a LMWH agent administered SC is reasonable. • Acute myocardial infarction and left ventricular thrombus: o Patients with ischemic stroke or transient ischemic attack in the setting of an acute myocardial infarction complicated by left ventricular mural thrombus formation should be treated with oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least three months. • Cardiomyopathy: o In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction, the benefit of warfarin has not been established. o Warfarin (INR, 2.0 to 3.0), aspirin (81 mg/day), clopidogrel (75 mg/day), or the combination of aspirin (25 mg twice-daily) plus extended-release dipyridamole (200 mg twice-daily) may be considered to prevent recurrent ischemic events in patients with pervious ischemic stroke or transient ischemic attack and cardiomyopathy. • Native valvular heart disease: o For patients with ischemic stroke or transient ischemic attack who have rheumatic mitral valve disease, whether or not atrial fibrillation is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0). o To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin. o For patients with ischemic stroke or transient ischemic attack

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	and native aortic or nonrheumatic mitral valve disease who do not have atrial fibrillation, antiplatelet therapy may be reasonable. o For patients with ischemic stroke or transient ischemic attack and mitral annular calcification, antiplatelet therapy may be considered. o For patients with mitral valve prolapse who have ischemic stroke or transient ischemic attack, long-term antiplatelet therapy may be considered. • Prosthetic heart valves: o For patients with ischemic stroke or transient ischemic attack who have mechanical prosthetic heart valves, warfarin is recommended with a target INR of 3.0 (range, 2.5 to 3.5). o For patients with prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/day in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high risk of bleeding. o For patients with ischemic stroke or transient ischemic attack who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR, 2.0 to 3.0) may be considered.

Conclusions

The injectable anticoagulants include low molecular weight heparin (LMWH) agents (dalteparin [Fragmin®] and enoxaparin [Lovenox®]) and factor Xa inhibitors (fondaparinux [Arixtra®]). The agents in both classes work by binding to antithrombin, causing inhibition of the clotting factors thrombin and factor Xa.[1-3] These agents have a greater inhibitory effect on factor Xa compared to thrombin.[4,5] Because the LMWH agents are prepared using different methods of depolymerization, the various agents in this class differ and are not clinically interchangeable.[5] Currently, enoxaparin and fondaparinux are the only injectable anticoagulants that are available generically.[6,7]

In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction; however, treatment for these indications will most likely be initiated in an acute hospital setting. Outpatient, or inpatient, administration of the injectable anticoagulants for prophylaxis and treatment of VTE may be appropriate depending on the specific clinical situation.[8] Evidence from clinical trials and recommendations from clinical guidelines support the use of the injectable anticoagulants in FDA-approved indications.[8-15,16-73] Several placebo-controlled trials have consistently demonstrated the efficacy of the injectable anticoagulants, but when compared to other methods of anticoagulation (e.g., heparin, rivaroxaban unfractionated heparin [UFH], warfarin), their "superiority" in terms of recurrent VTE and safety has not always been demonstrated.[26-31,34-53,53,65-74] The evidence from these trials support the current clinical guidelines which recommend any of these methods as appropriate treatment options.[8] When comparing fondaparinux to the LMWH agents, treatment with fondaparinux has demonstrated "superiority" in terms of the incidence of VTE in the majority of clinical trials, while demonstrating a comparable rate of major bleeding.[56-61] However, data from two clinical trials revealed no difference between treatment with fondaparinux compared to dalteparin or enoxaparin in the development of VTE.[56,60]

LMWH, fondaparinux, apixaban (Eliquis®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), low dose unfractionated heparin (UFH), adjusted-dose vitamin K antagonist (VKA) therapy, aspirin, or an

intermittent pneumatic compression device are recommended as options for thromboprophylaxis in total hip or knee arthroplasty. LMWH, fondaparinux, low dose UFH, adjusted-dose VKA therapy, aspirin, or an intermittent pneumatic compression device are recommended as options for thromboprophylaxis in hip fracture surgery. Of these therapies, LMWH is preferred to the other recommended thromboprophylaxis agents for these orthopedic surgeries. Thromboprophylaxis for orthopedic surgeries should be administered for a minimum of 10 to 14 days, and extended up to 35 days from the day of surgery for major orthopedic surgeries. LMWH and low dose UFH are both recommended as options for thromboprophylaxis in non-orthopedic surgical patients (general and abdominal-pelvic surgery) at moderate to high risk for VTE and who are not at high risk for bleeding complications, while LMWH, low dose UFH, and fondaparinux are recommended in acutely ill hospitalized patients at increased risk of thrombosis (i.e., non-surgical patients). Parenteral anticoagulation (LMWH, fondaparinux, or UFH) is recommended for a minimum of five days for the treatment of acute deep vein thrombosis or pulmonary embolism, accompanied by early initiation of VKA therapy. With regards to parenteral anticoagulation for acute deep vein thrombosis or pulmonary embolism, LMWH or fondaparinux is preferred over UFH. Duration of anticoagulation after treatment of an acute thromboembolic event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor, and if it was the first or second thromboembolic event.[8] In general, recommendations from other clinical guidelines are in line with the recently updated American College of Chest Physicians guideline.[9-11]

References

1. Fragmin® [package insert]. New York (NY): Pfizer Inc; 2010 Oct.
2. Lovenox® [package insert]. Greenville (NC): Sanofi-aventis U.S. LLC; 2013 Jun.
3. Arixtra® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2012 Jan.
4. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98.
5. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:141S-59S.
6. FDA approves first generic enoxaparin sodium injection [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2010 Jul 23 [cited 2013 Jul 2]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm.
7. FDA OKs Dr. Reddy's generic version of Arixtra [article on the internet]. New York City (NY): Bloomberg L.P.; 2011 Jul 13 [cited 2013 Jul 2]. Available from: http://www.businessweek.com/ap/financialnews/D9OET16G0.htm.
8. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(Suppl 2):7-47.
9. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg NA, Goldhaber SZ, et al; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011 Apr 26;123(16):1788-830.
10. National Institute for Health and Clinical Excellence (NICE). Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital [guideline on the Internet]. NICE: 2010 [cited 2013 Jul 2]. Available from: http://guidance.nice.org.uk/CG92.
11. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29;61(4):485-510.
12. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jun 11;61(23):e179-347.
13. Hamm CW, Bassand JP, Agewell S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology. Eur Heart J. 2011 Dec;32(23):2999-3054.
14. Kushner FG, Hand M, Smith SC, King III SB, Anderson JL, Antman EM, et al. 2009 Focused update: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120:2271-306.
15. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary. J Am Coll Cardiol. 2004;44:671-719.

16. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSNCE meta-analysis. Circulation. 1999;100:1602-8.
17. Murphy SA, Gibson CM, Marrow DA, Van de Werf F, Menown IB, Goodman SG, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared to unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28:2077-86.
18. Magee K, Sevcik WW, Moher D, Rowe BH. Low molecular weight heparins vs unfractionated heparin for acute coronary syndromes. Cochrane Database of Systematic Reviews. 2003, Issue 1. Art. No.:CD002132. DOI:10.1002/14651858.CD002132.
19. Malhotra S, Karan RS, Bhargava VK, Pandhi P, Grover A, Sharma YP, et al. A meta-analysis of controlled clinical trials comparing low-molecular weight heparins with unfractionated heparin in unstable angina (abstract). Indian Heart J. 2001;53(2):197-202.
20. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet. 2000;355:1936-42.
21. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin vs a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53.
22. Lee AYY, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol. 2005;23:2123-9.
23. Akl EA, Labedi N, Barba M, Terrenato I, Sperati F, Muti P, Schünemann H. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD006650. DOI: 10.1002/14651858.CD006650.pub3.
24. Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Rutjes AWS. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008500. DOI:10.1002/14651858.CD008588.pub2.
25. Douketis J, Cook D, Meade M, Guyatt G, Geerts W, Skrobik Y, et al. Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin. An assessment of safety and pharmacodynamics: the DIRECT Study. Arch Intern Med. 2008;168(16):1805-12.
26. Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low-molecular weight heparin. Arthroscopy. 2002;18(3):257-63.
27. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejo Bro JP, Anderson G, et al. Efficacy and safety of prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) after total hip arthroplasty-The Danish Prolonged Prophylaxis (DaPP) Study. Throm Res. 1998;89:281-7.
28. Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-9.
29. Torholm C, Broeng L, Seest Jorgensen P, Bjerregaard P, Josephsen L, Korsholm Jorgensen P, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. J Bone Joint Surg (Br). 1991;73-B:434-8.
30. Francis CW, Pellegrini VD, Totterman S, Boyd AD, Marder VJ, Liebert KM, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am. 1997;79:1365-72.
31. Eriksson BI, Kalebo P, Anthymyr BA, Wadenvik H, Tengborn L, Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. J Bone Joint Surg Am. 1991;73:484-93.
32. Krotenberg R, Adler U, Pomeranz B, Miller JD, Russell MW. Dalteparin vs enoxaparin in prophylaxis for deep-vein thrombosis after total hip or knee arthroplasty. A retrospective analysis. Am J Phys Med Rehabil. 2001;80:889-95.

33. Spiro TE, Johnson GJ, Christie MJ, Lyons RM, MacFarlane DE, Blasier RB, et al. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Ann Intern Med. 1994;121:81-9.
34. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975-80.
35. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Nicol P, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility. Ann Intern Med. 2010;153:8-18.
36. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793-800.
37. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. Blood Coagul Fibrinolysis. 2003;14:341-6.
38. Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al. Low-molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.
39. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomized comparison of enoxaparin vs placebo. Lancet. 1996;348:224-8.
40. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci. 2008;13:442-51.
41. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman M, Kakkar AK, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-75.
42. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban vs short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial. Lancet. 2008 Jul 5;372(9632):31-9.
43. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2776-86.
44. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. Lancet. 2009 May 16;373(9676):1673-80.
45. Colwell CW, Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am. 1999;81:932-40.
46. Fitzgerald RH, Spiro TE, Trowbridge AA, Gardiner GA, Whitsett TL, O'Connell MB, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am. 2001;83:900-6.
47. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, l'Esperance B, Demers C, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med. 1996;124:619-26.
48. No authors listed. Low-molecular-weight heparin (enoxaparin) vs dextran 70. The prevention of postoperative deep vein thrombosis after total hip replacement. Arch Intern Med. 1991;151:1621-4.
49. Senaran H, Acaroglu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. Arch Orthop Trauma Surg. 2006;126:1-5.
50. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin vs low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Ann Surg. 2001;233(3):438-44.

51. Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Floshbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J. 2003;145:614-21.
52. De A, Roy P, Garg VK, Pandey NK. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. Blood Coagul Fibrinolysis. 2010;21:57-61.
53. Colwell CW, Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Balham JD, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 1994;76:3-14.
54. Simonneau G, Laporte S, Mismetti P, Derlon A, Samii K, Samama SM, et al. A randomized study comparing the efficacy and safety of nadroparin 2,850 IU (0.3 mL) vs enoxaparin 4,000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. J Thromb Haemost. 2006;4:1693-700.
55. 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;163:1337-42.
56. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux vs perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212-20.
57. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux vs preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomized double-blind comparison. Lancet. 2002;359:1715-20.
58. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-10.
59. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-304.
60. Turpie AFF, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux vs postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomized double-blind trial. Lancet. 2002;359:1721-6.
61. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. Arch Intern Med. 2002;162:1833-40.
62. Eikelboom JW, Quinlan DJ, O'Donnell M. Major bleeding, mortality and efficacy of fondaparinux in venous thromboembolism prevention trials. Circulation. 2009;120;2006-11.
63. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. Thromb Haemost. 2004;92:747-51.
64. van Dongen CJ, Mac Gillavry MR, Prins MH. Once vs twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2005, Issue 3. Art. No.:CD003074. DOI:10.1002/14651858.CD003074.pub2.
65. Testroote M, Stigter WAH, de Visser DC, Janzing HMJ. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database of Systematic Reviews. 2008, Issue 4. Art. No.:CD006681. DOI:10.1002/14651858.CD006681.pub2.
66. van der Heijden JF, Hutten BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term management of symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2001, Issue 3. Art. No.:CD002001. DOI:10.1002/14651858.CD002001.
67. Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors vs vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. Cochrane Database of Systematic Reviews. 2010, Issue 4. Art. No.:CD005981. DOI:10.1002/14651858.CD005981.pub2.

68. Erkens PMG, Prins MH. Fixed dose subcutaneous low molecular weight heparins vs adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database of Systematic Reviews. 2010, Issue 9. Art. No.:CD001100. DOI:10.1002/14651858.CD001100.pub3.
69. Othieno R, Abu Affan M, Okpo E. Home vs in-patient treatment for deep vein thrombosis. Cochrane Database of Systematic Reviews. 2007, Issue 3. Art. No.:CD003076. DOI:10.10002/14651858.CD003076.pub2.
70. Kanaan AO, Silva MA, Donovan JL, Roy T, Al-Homsi AS. Meta-analysis of venous thromboembolism prophylaxis in medically ill patients. Clin Ther. 2007;29(11):2395-405.
71. Handoll HHG, Farrar MJ, McBirnie J, Tytherleigh-Strong GM, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database of Systematic Reviews. 2002, Issue 4. Art. No.:CD000305. DOI:10.1002/14651858.CD000305.
72. Rasmussen MS, Jorgensen LN, Willie-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database of Systematic Reviews. 2009, Issue 1. Art. No.: CD004318. DOI:10.1002/14651858.CD004318.pub2.
73. Brookenthal KR, Freedman KB, Lotke PA, Fitzgerald RH, Lonner JH. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. J Arthroplasty. 2001;16(3):293-300.
74. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172(5):397-402.
75. Fondaparinux: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 2]. Available from: http://www.utdol.com/utd/index.do.
76. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Jul 2]. Available from: http://online.factsandcomparisons.com.
77. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. J Am Coll Cardiol. 2011 Dec 6;58(24):e44-122.
78. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 Jan;42(1):227-76.