Department of Vermont Health Access

Therapeutic Class Review
Injectable Anticoagulants

Overview/Summary

The injectable anticoagulants include low molecular weight heparin (LMWH) agents and factor Xa inhibitors. In general, the injectable anticoagulants are Food and Drug Administration (FDA) approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Of note, some of the 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 of the injectable anticoagulants are outlined in Table 2.[1-4]

The LMWH agents include dalteparin (Fragmin®), enoxaparin (Lovenox®) and tinzaparin (Innohep®). These agents exert their anticoagulant 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.[5,6] Fondaparinux (Arixtra®) 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.[6] Currently, enoxaparin is the only injectable anticoagulant that is available generically.[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.[6]

The current clinical guidelines support the use of the injectable anticoagulants for their FDA approved indications.[8-12] According to the American College of Chest Physicians, the routine use of a LMWH agent, fondaparinux or a vitamin K antagonist (VKA) is recommended for the prevention of VTE in patients undergoing an orthopedic surgery, with only a LMWH agent recommended in high risk patients who are undergoing knee arthroscopy specifically. Thromboprophylaxis with one of these agents in patients undergoing orthopedic surgery should be continued for at least ten days. Extended prophylaxis (up to 35 days) is recommended in patients undergoing total hip and knee replacement surgery, as well as hip fracture surgery. For the prevention of VTE in acutely ill medical patients, LMWH agents, low dose UFH and fondaparinux are recommended, while LMWH agents and VKAs are recommended in patients with cancer. For the treatment of an acute deep vein thrombosis (DVT), anticoagulation should be initiated with a LMWH agent, UFH or fondaparinux. Therapy with these agents typically lasts for at least five days, until the International Normalized Ratio is at least 2.0 or greater for 24 hours, and it is recommended that a VKA, together with one of these agents, be initiated on the first day of treatment. Anticoagulation therapy with a VKA typically lasts for a period of three months in these patients; however, extended therapy may be required. Because patients with cancer are at high risk, it is recommended that initial treatment of an acute DVT with a LMWH agent continue for the first three to six months, followed by indefinite therapy with either a VKA or LMWH agent. Recommendations for treatment of an acute pulmonary embolism are the same as those for an acute DVT.[8]

Clinical guidelines also recommend the use of a LMWH agent, fondaparinux, UFH or bivalirudin (direct thrombin inhibitor) for the management of a non-ST-segment elevated acute coronary syndrome (NSTE ACS). 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. Additionally, it appears that fondaparinux has a more favorable safety and efficacy profile compared to the LMWH agents in certain clinical situations,

including patients at high risk for bleeding. While all of the pertinent clinical guidelines recommend a LMWH agent as an appropriate option for anticoagulation, it appears that enoxaparin has the most established evidence for this indication.[9,10] LMWH agents and fondaparinux are also recommended anticoagulant therapies in acute STEMIs.[11,12]

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	-
Tinzaparin (Innohep®)	Injectable anticoagulants/low molecular weight heparin	-

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

Indications

As mentioned previously, in general, the injectable anticoagulants are Food and Drug Administration (FDA) approved for prophylaxis and/or treatment of venous thromboembolism (VTE).[1-4] Of note, enoxaparin, a low molecular weight heparin (LMWH) agent, currently has the most FDA approved indications of the agents in this class, and is the only injectable anticoagulant FDA approved for the treatment of acute ST-segment elevation myocardial infarction.[2] Both enoxaparin and dalteparin, another LMWH agent, are FDA approved for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarctions.[1,2] Dalteparin is also the only LMWH agent not FDA approved for the treatment of VTE and is the only agent in the class that is FDA approved for the extended treatment of symptomatic VTE in patients with cancer.[1] Of note, the LMWH agent tinzaparin has one FDA approved indication for the treatment of acute deep vein thrombosis. The safety and efficacy of tinzaparin for this indication were established in hospitalized patients only.[4]

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

Indication	Dalteparin	Enoxaparin	Fondaparinux	Tinzaparin
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.
** With or without pulmonary embolism 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[13]

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
Tinzaparin	86.7	Primary (% not reported)	Not reported	3 to 4

Clinical Trials

The evidence demonstrating the safety and efficacy of the injectable anticoagulants in their respective Food and Drug Administration (FDA) approved indications is well established, and as mentioned previously, clinical guidelines support the use of these agents in these indications.[8-12,14-71] Due to the fact that for a number of the FDA approved indications, treatment with an injectable anticoagulant will be initiated in an acute hospital setting, only meta analyses and Cochrane Reviews demonstrating the safety and efficacy of these agents for those indications are included in Table 4.[14-18] 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.[19-71] It can be assumed that for this FDA approved indication, treatment is more likely to be administered as an outpatient, as recommended per the current clinical treatment guidelines.[8]

Currently, dalteparin is the only injectable anticoagulant FDA 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 in dalteparin-treated patients at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow up of these patients revealed a significant benefit in mortality with dalteparin in patients without known metastases of their cancer.[19,20] 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 significant difference was observed when treatment with a LMWH agent was compared to fondaparinux for reducing the incidence of recurrent VTE, as well as for the incidence of major and minor bleeding events. This review also compared two individual LMWH agents, dalteparin and tinzaparin, and no significant 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.[21] Of note, while dalteparin is the only LMWH agent to have FDA approval for the extended treatment of symptomatic VTE in patients with cancer, the American College of Chest Physicians (ACCP) does not distinguish among the various agents in their recommendations, stating that initial treatment with a LMWH agent should be continued for the first three to six months of long term anticoagulant therapy. In addition, the ACCP recommends against the routine use of thromboprophylaxis for the primary prevention of VTE in cancer patients receiving chemotherapy or hormone therapy. Routine use of primary thromboprophylaxis also should not be used to improve survival in patients with cancer.[8]

The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established.[22-71] 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.[23-26,31-37,48,63,71] When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis (e.g., heparin, UFH, warfarin), “superiority” in terms of recurrent VTE and safety is not always consistent, which supports recommendations from current clinical guidelines.[27,28,38-46,60,64-70] For treatment and thromboprophylaxis in these patients, any of these options may be appropriate.[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.[50-53] 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.[54] Another trial noted no difference between fondaparinux and dalteparin for the incidence of VTE and major bleeding.[49]

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[14] 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[15] 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
UFH			by 30 days (or the closest time point available to 30 days) Secondary: The individual endpoints of the composite endpoint	patients (12.5 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).
Cochrane Review (Magee et al)[16] LMWH vs	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	Primary: Death, MI, recurrent angina, revascularization procedures, major hemorrhage,	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
UFH	72 hours of presentation	>14 days)	minor hemorrhage, thrombo-cytopenia, allergic reactions Secondary: Not reported	0.70 to 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Thrombocytopenia was a relatively rare event in the four trials that reported this 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)[17] LMWH (excluding enoxaparin) vs UFH	MA (5 RCTs) Patients with unstable angina	N=not reported Not reported	Primary: Composite of death, MI, recurrent angina and urgent revascularization; composite of major hemorrhage, minor hemorrhage, thrombo-cytopenia, 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[18] UFH vs LMWH	MA (12 RCTs) Patients with unstable angina or non-Q-wave MI, receiving ASA	N=17,157 Duration varied (short and long term treatment)	Primary: Composite of death or MI, major bleeding Secondary: Recurrent angina, need for	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or no treatment			revascularization	*Short term LMWH vs placebo or no treatment* Pooled analysis from two trials (n=1,639) revealed that overall, treatment with 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 treated 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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[19] 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	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
anticoagulant received dalteparin initially for 5 to 7 days.				
Lee et al[20] 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 5 to 7 days.	Post hoc analysis of Lee et al[18] 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
Cochrane Review (Akl et al)[21] LMWH vs UFH vs fondaparinux	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, thrombo-	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A total of 16 RCTs were included: 13 comparing LMWH to UFH, 2 comparing fondaparinux to heparin and 1 comparing dalteparin to tinzaparin.			cytopenia	Secondary: *LMWH vs UFH* 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.
Prophylaxis and/or Treatment of Venous Thromboembolism				
Douketis et al[22] 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	insufficiency			prophylaxis was 18.9 (6.4) and 28.4 (17.3) mL/min, respectively (*P* value not reported). Secondary: Not reported
Michot et al[23] Dalteparin 2,500 units SC once, followed by 2,500 to 5,000 units SC QD vs no treatment Patients in the control group were given no medical prophylaxis against thromboembolism.	PRO, RCT, SB Patients 18 to 80 years of age referred to an institution for diagnostic or therapeutic arthroscopic knee surgery as outpatients	N=218 Up to 30 days	Primary: Incidence of DVT, safety Secondary: Not reported	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. 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[24] Dalteparin vs placebo All patients received dalteparin 5,000 units SC QD for 7 days after the surgery.	DB, PG, PRO, RCT Patients >18 years of age admitted to the hospital for THA	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Leizorovicz et al[25] Dalteparin 5,000 units SC QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with an acute medical condition requiring a projected hospitalization of ≥4 days and had ≤3 days of prior immobilization	N=2,991 14 days	Primary: Incidence of VTE and sudden death by day 21 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 thrombo-cytopenia by day 21; symptomatic VTE at day 90	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). 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[26] Dalteparin 2,500 units SC QD twice, followed by	PC, RCT Patients >40 years of age	N=112 7 days	Primary: DVT, safety Secondary:	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5,000 units SC QD vs placebo	admitted for THR		Not reported	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: Not reported
Francis et al[27] 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 THA	N=580 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[28] Dalteparin 5,000 units SC QD vs UFH 5,000 units SC QD	DB, PRO, RCT Patients ≥40 years of age undergoing elective THR	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. 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[29] Dalteparin vs enoxaparin	RETRO Patients who underwent TKA or THA and received enoxaparin, dalteparin or ASA as DVT prophylaxis at the institution where their TKA or THA was performed and who received enoxaparin or dalteparin as DVT prophylaxis during their rehabilitation stay	N=934 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Spiro et al[30] Enoxaparin 10 mg SC QD vs enoxaparin 40 mg SC QD vs enoxaparin 30 mg SC BID	DB, MC, PG, RCT Patients ≥31 years of age who were scheduled for hip replacement surgery	N=572 7 days	Primary: Venous thrombosis by day seven, hemorrhagic complications Secondary: Not reported	Primary: The incidence of DVT was 25, 14 and 11% among 10 mg-, 40 mg- and 30 mg-treated patients. A significantly higher incidence of DVT occurred with 10 mg compared to either 40 (*P*=0.02; OR, 2.16; 95% CI, 1.21 to 4.10) or 30 mg (*P*<0.001; OR, 2.93; 95% CI, 1.48 to 5.81). There was no difference in the incidence of DVT with 30 mg compared to 40 mg (*P*>0.2; OR, 1.36; 95% CI, 0.73 to 2.53). The overall incidence of hemorrhagic episodes with 10 mg (5%) was significantly lower than with 30 mg (13%; *P*<0.05). The incidence of hemorrhagic episodes was similar between 40 and 30 mg (11 vs 13%; *P* value not reported). The overall incidence of major hemorrhage was low with all three doses. Secondary: Not reported
Bergqvist et al[31] 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) (*P*=0.02; 95% CI, 10 to 82). 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; *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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hull et al[32] Enoxaparin 40 mg SC QD vs placebo All patients received enoxaparin 40 mg SC QD for 10±4 days before randomization.	DB, MC, PG Patients ≥40 years of age with acute medical illness, a life expectancy of ≥6 months and had recently reduced mobility for up to 3 days	N=7,500 6 months (28±4 days of treatment)	Primary: VTE, major hemorrhagic complications Secondary: VTE incidence through three months; mortality at one, three and six months; major and minor hemorrhagic complications, serious adverse events, thrombo-cytopenia	Primary: At 28±4 days, treatment with enoxaparin significantly reduced the risk of VTE (2.5 vs 4.0%; absolute risk difference, -1.53%; 95% CI, -2.54 to -0.52), an effect largely attributable to a decrease in symptomatic DVT (absolute risk difference, -0.60%; 95% CI, -1.00 to -0.19). The number of major hemorrhages at 30 days was significantly greater in enoxaparin-treated patients (0.8 vs 0.3%; absolute risk difference, 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 (absolute risk difference 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 bleeding events (major and minor) (absolute risk difference 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[33] 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	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	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	who were not immobilized for >3 days		and minor hemorrhage, thrombo-cytopenia, other adverse events	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. The risk of death was nonsignificantly reduced with treatment 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). 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[34] Enoxaparin 20 or 40 mg SC QD vs placebo	Post hoc analysis of Samama et al[32] 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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; *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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Bergqvist et al[35] Enoxaparin vs placebo All patients received enoxaparin 40 SC QD for 7 to 11 days before randomization.	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: seven vs 24% (OR, 0.43; 95% CI, 1.9 to 10.0; *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). 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[36] 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 THR or conversion or revision THR 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[37] Enoxaparin 20 mg SC QD	2 DB, MC, PC, PG, RCTs	N=771 90 days	Primary: VTE within 72 hours after	Primary: In patients undergoing THA, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs enoxaparin 40 mg SC QD vs enoxaparin 20 mg SC BID vs placebo	Patients ≥20 years of age undergoing elective THA or TKA	(14 days of treatment)	completion or discontinuation of treatment, any bleeding Secondary: Adverse events	placebo-, enoxaparin 20 mg QD-, enoxaparin QD 40 mg- and enoxaparin 20 mg BID-treated patients. 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 THA 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 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 TKA, 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. 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 THA 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 TKA the incidence of all adverse events was 98.9 vs 100% in placebo- and enoxaparin-treated patients (*P*=0.377).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Colwell et al[38] 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[39] 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 TKA	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[40] 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; corresponding to a RRR of 28.6% (95% CI, 11.1 to 43.1) with enoxaparin treatment (*P*=0.003). The absolute risk difference 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 absolute risk difference was 0.3% in favor of warfarin (95% CI, -2.4 to 1.8). Secondary: Not reported
No authors listed (The Danish Enoxaparin Study Group)[41] 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 THR	N=283 7 to 11 days	Primary: DVT, bleeding Secondary: Not reported	Primary: DVT was diagnosed in a total of 31 patients; seven out of 108 and 24 out of 11 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[42] 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[43] 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, thrombo-cytopenia 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[44] 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[45] 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 days of	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 gastrointestinal bleeding compared to 18 (24%) UFH-treated patients who

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hospitalization			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[46] 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[47] Enoxaparin 40 mg SC QD vs nadroparin* 2,850 units SC QD	DB, DD, MC, PG, PRO, RCT Patients undergoing elective resection of colorectal	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	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:

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.	adenocarcinoma		and distal asymptomatic 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; thrombo-cytopenia; other adverse events	There was a higher incidence of distal DVT in nadroparin-treated patients (12.5 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[48] Fondaparinux 2.5 mg SC QD vs placebo All patients received OL fondaparinux 2.5 mg SC QD for up to 6 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	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and neck if surgery was planned within 48 hours after admission			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). 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[49] Fondaparinux 2.5 mg SC QD vs dalteparin 2,500 units once, followed by 5,000 units SC QD Treatment was scheduled to last up to 5 to 9 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; thrombo-cytopenia; 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lassen et al[50] Fondaparinux 2.5 mg SC QD vs enoxaparin 40 mg SC QD Treatment was scheduled to last up to 5 to 9 days.	DB, RCT Patients ≥18 years of age scheduled for primary elective THR surgery or revision of ≥1 component of a previously implanted total hip prosthesis	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; symptomatic VTE up to day 11; symptomatic VTE up to day 49; death; other bleeding; transfusion requirements; thrombo-cytopenia; any other adverse events	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). 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[51] Fondaparinux 2.5 mg SC QD vs enoxaparin 30 mg SC BID Treatment was scheduled to last up to 5 to 9 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;	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			symptomatic VTE up to day 49; death; other bleeding; a need for transfusion; thrombo-cytopenia; any other adverse event	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 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[52] Fondaparinux 2.5 mg SC QD vs enoxaparin 40 mg SC QD Treatment was scheduled to last up to 5 to 9 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, thrombo-cytopenia	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Turpie et al[53] Fondaparinux 2.5 mg SC QD vs enoxaparin 30 mg SC BID Treatment was scheduled to last up to 5 to 9 days.	DB, MC, RCT Patients ≥18 years of age undergoing a first elective THR or a revision of ≥1 component of a previously implanted total hip prosthesis	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 distal DVT or symptomatic VTE up to day 11; symptomatic VTE up to day 49; death; minor bleeding; need for transfusion; thrombo-cytopenia	Primary: By day 11, the proportion of patients who developed VTEs was lower in fondaparinux-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). 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. 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 3.1; *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[54] Fondaparinux vs enoxaparin	MA (4 DB, MC, RCT) Patients ≥18 years of age who were scheduled for primary elective THR surgery or revision of ≥1 component of a previously	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 (6.8 vs 13.7%; common odds reduction, 55.2%; 95% CI, 45.8 to 63.1; *P*<0.001). In THR, 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	implanted total hip prosthesis, elective major knee surgery or standard surgery for fracture of the upper third of the femur, including femoral head and neck			Overall, there were 96 major bleeding events among the 3,616 fondaparinux-treated patients compared to 63 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 patients compared to eight 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: 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[55] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				more likely to receive treatment with fondaparniux. Secondary: Not reported
Jorgensen et al[56] Tinzaparin 3.5 units SC QD vs no treatment	MC, RCT, SB Patients >18 years of age with planned plaster cast on a lower extremity for ≥3 weeks irrespective of diagnosis	N=300 Not reported	Primary: Incidence of DVT Secondary: Not reported	Primary: Ninety five patients did not reach objective endpoint due to various reasons such as discontinuing treatment or not fulfilling the trial. The mean duration of treatment with self injection of tinzaparin was 5.5 weeks. Ninety nine and 106 tinzaparin-treated and no treatment patients reached the venographic endpoint. DVT was found in 10 and 18 tinzaparin-treated and no treatment patients (*P*=0.15), corresponding to an OR of 0.55 (95% CI, 0.34 to 1.26). Secondary: Not reported
Romera et al[57] Tinzaparin 175 anti-Xa units/kg SC QD vs tinzaparin 175 anti-Xa units/kg SC QD plus acenocoumarol* 3 mg Patients receiving acenocoumarol* had their dose adjusted to maintain an INR between 2.0 to 3.0. Tinzaparin was discontinued in these patients when the INR reached ≥2.0 on 2	OL, PRO, RCT Patients >18 years of age referred to the vascular surgery department of the hospital with a first episode of acute proximal-vein thrombosis of the lower limbs (onset of symptoms <2 weeks)	N=241 12 months (6 months of treatment)	Primary: First episode of symptomatic DVT or PE at six and 12 months, major bleeding Secondary: Not reported	Primary: At six months, 4.2 vs 5.7% tinzaparin- and tinzaparin plus acenocoumarol-treated patients had a new symptomatic VTE event (*P*=0.6). At one year, 5.00 vs 10.65% had new episodes of symptomatic VTE (*P*=0.11; 95% CI, -12.4 to 1.1). Three (2.5%) and one (0.8%) tinzaparin plus acenocoumarol- and tinzaparin-treated patients had major bleeding (*P*=0.6). There were no fatal bleeding events and minor bleeding events were not registered. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
consecutive measurements.				
Smith et al[58] Phase 1: Tinzaparin 50 to 175 anti-Xa units/kg SC QD Phase 2 (continued until pregnancy): tinzaparin, maintenance dose was established when 2, 4-hour postdose anti-Xa levels were recorded in the target range, 1 week apart within the first 4 weeks of treatment. During this time tinzaparin dosage was adjusted as necessary to maintain target range 4-hour postdose anti-Xa activity Phase 3: warfarin, initiated 1 to 2 days post partum and continued for at least the first 6 postpartum weeks. In Phase 3, tinzaparin was discontinued when adequate anticoagulation was established.	MC, noncontrolled, OL, PRO Patients >18 years of age who were pregnant or wishing to become pregnant, requiring anticoagulation eight for the treatment of VTE or for thrombo-prophylaxis	N=54 Duration varied	Primary: Determine whether a dose adjustment is necessary as gestation progresses Secondary: Incidence of thrombotic, hemorrhagic and thrombo-cytopenic or other adverse events	Primary: One (3.4%) 175 anti-Xa units/kg-treated patient and three (20%) 50 anti-Xa units/kg-treated patients required a dose increase during the initial dose titration in phase one to achieve target anti-Xa activity. Considering all anti-Xa 4-hour assessments, there was insufficient evidence to conclude that gestation week influences anti-Xa activity for the moderate risk group (*P*=0.22). For the high risk treatment patients, there was significant evidence to suggest that gestation week influences anti-Xa (*P*=0.01). The estimated reduction in anti-Xa over a 24 week gestation period, assuming the patient remains on a constant dose of tinzaparin during this time, is 0.10 units/mL (95% CI, 0.03 to 0.18). During the second phase, the only case requiring a tinzaparin dose increase to maintain anti-Xa activity within target range was a 175 units/kg/day-treated patient. Secondary: During the trial, two patients had adverse events that might possibly have suggested thromboembolic complication. One patient had a severe adverse event, 12 patients had moderate and 27 had mild adverse events where a causal relationship to tinzaparin could not be ruled out. Most of these events comprised bleeding or bruising at the injection site and mucocutaneous bleeding.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daskalopoulos et al[59] Tinzaparin 175 anti-Xa units/kg SC QD vs conventional antithrombotic therapy Patients assigned to conventional therapy received an IV bolus of 5,000 units of UFH immediately upon admission to the hospital, which was continued for 5 to 7 days. Oral acenocoumarol* was started on the 3rd day following UFH therapy and adjusted to maintain an INR between 2.0 to 3.0. Patients assigned to tinzaparin did not get hospitalized.	OL, PRO, RCT Patients >18 years of age who had been referred to an accident and emergency department of a district hospital with acute proximal DVT of the lower limbs (onset of symptoms <1 week)	N=102 12 months (6 months of treatment)	Primary: Recanalization of the thrombosed veins, development in the affected veins, overall incidence of major events Secondary: Recurrent VTE, major and minor hemorrhagic complications, mortality	Primary: Regarding the degree of thrombus regression, total score reduction (representing thrombus regression), was observed with both treatments and remained constant in all follow up assessments. However, a more rapid recanalization was achieved with tinzaparin treatment; these differences reached significance at three (*P*=0.017), six (*P*=0.013) and 12 months (*P*=0.011). Reflux patterns detected at all assessments worsened equally in time but did not differ between the two treatments, although there was a trend in favor of treatment with tinzaparin (*P* values not significant). The overall incidence of major events was significantly lower in tinzaparin-treated patients (14.0 vs 32.7%; *P*=0.0354). Secondary: During the treatment period, two (4.0%) cases of recurrent DVT in tinzaparin-treated patients and three (5.8%; *P* value not significant) in conventional antithrombotic therapy-treated patients were identified. Overall, in the whole trial period, DVT recurrence was observed in 6.0 vs 9.6% tinzaparin- and conventional antithrombotic therapy-treated patients (*P* value not reported). One single incidence of symptomatic PE was diagnosed in a conventional antithrombotic therapy-treated patient, which was fatal. There were no significant differences in bleeding complications between the two treatments (major bleeding: 4.0 vs 7.7%; *P* value not significant; minor bleeding: 6.0 vs 5.8%; *P* value not significant). During the 12 month period, the rate of death was 4.0 vs 9.6% in tinzaparin- and conventional antithrombotic therapy-treated patients.
Hull et al[60] Tinzaparin 175 anti-Xa units/kg SC QD	MC, OL, RCT Cancer patients ≥18 years of age with acute	N=200 12 months (12 weeks of treatment)	Primary: Recurrent VTE, death, bleeding Secondary:	Primary: At 12 months UFH plus warfarin-treated patients had an excess of recurrent VTE compared to tinzaparin-treated patients (16.0 vs 7.0%; *P*=0.044; RR, 0.44; absolute difference, -9.0%; 95% CI, -21.7 to -0.7).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs UFH 5,000 units IV bolus or 80 units/kg, followed by a continuous IV infusion plus warfarin 5 to 10 mg started on day 1 Warfarin doses were adjusted to maintain an INR between 2.0 to 3.0.	proximal-vein thrombosis		Not reported	At 12 months, 47 (47%) and 47 (47%) tinzaparin and UFH plus warfarin-treated patients died (absolute difference, 0.0%; 95% CI, -14.6 to 13.2). Death was insidious due to progressive cancer for most patients who died in either group. Bleeding occurred in 27 vs 24% of tinzaparin- and UFH plus warfarin-treated patients (absolute difference, -3.0%; 95% CI, -9.1 to 15.1). Secondary: Not reported
Oran et al[61] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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
Cochrane Review (van Dongen et al)[62] LMWH QD vs LMWH BID	5 RCTs Patients with VTE receiving initial treatment	N=1,508 Duration varied	Primary: Symptomatic recurrent VTE, major hemorrhagic 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	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). 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 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.
Cochrane Review (Testroote et al)[63] LMWH vs no treatment or placebo	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Cochrane Review (van der Heijden et al)[64] VKAs vs LMWH	7 RCTs Patients with symptomatic DVT receiving long term treatment	N=1,137 3 to 9 months	Primary: Incidence of recurrent symptomatic VTE, occurrence of major bleeding complications, and 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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Cochrane Review (Salazar et al)[65] DTI (dabigatran†, desirudin, ximelagatran*) vs warfarin or LMWH (dalteparin, enoxaparin)	12 RCTs Patients who have undergone THR or TKR	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, and appearance of other serious adverse effects associated with treatment Secondary: Incidence of distal VTE, presence of hepatopathy after treatment, and morbidity associated with treatment	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 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 THR (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 THR (2,370 out of 5,949 vs 1,374 out of 4,378; OR, 1.40; 95% CI, 1.06 to 1.85).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Trials that began anticoagulation before surgery demonstrate 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				All-cause mortality, transaminase levels and blood loss were not evaluated.
Cochrane Review (Erkens et al)[66] LMWH vs UFH	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 within 48 hours after treatment cessations, overall mortality at the end of follow up	Primary: The occurrence of symptomatic VTE was evaluated during the initial treatment period, at three months follow up 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: 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Cochrane Review (Othieno et al)[67] LMWH vs UFH (in-patient use only) The patients were either randomized to home or in-patient treatment.	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, cost/incidence of treatment complications Secondary: Not reported	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 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[687] LMWH/fondaparinux vs	MA (9 RCTs) Medically ill patients with risk factors for VTE who had been	N=12,391 Duration varied	Primary: VTE, DVT, fatal or nonfatal PE, major or minor bleeding, fatal bleeding, VTE-	Primary: Treatment with 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 treatment with LMWH and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
UFH	followed for up to 7 to 21 days		related death Secondary: Not reported	UFH was found in reducing the incidence of VTE (OR, 0.89; 95% CI, 0.54 to 1.46). DVT events were significantly reduced in LMWH/fondaparinux-treated patients compared to placebo (OR, 0.60; 95% CI, 0.47 to 0.75; *P*≤0.001) and were 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 treatment with 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 treatment with 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 treatment with LMWH/fondaparinux was compared to placebo (OR, 0.54; 95% CI, 0.28 to 1.05). This finding remained consistent when treatment with 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). Treatment with 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 treatment with 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 3.4); 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When minor and major bleeding events were combined, a significant increase in the incidence of any bleeding was shown when comparing treatment with 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 treatment with 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 treatment with 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 treatment with 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
Cochrane Review (Handoll et al)[69] Injectable anticoagulants (LMWH, UFH) vs physical agents (compression stockings, arteriovenous foot pumps) vs placebo or no treatment	31 RCTs Patients undergoing surgery for proximal femoral fracture	N=2,958 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:	Primary: *Any heparin vs control/placebo* Out of 15 trials, there was a significant reduction in incidence of any DVT when treatment with 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 (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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment modalities were also compared to each other.			Not reported	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 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 treatment with 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
Cochrane Review (Rasmussen et al)[70] LMWH vs UFH vs mechanical methods vs VKAs (acenocoumarol* or phenprocoumon*)	4 RCTs Patients undergoing general abdominal or pelvic surgery for cancer or benign disease receiving prolonged thrombo-prophylaxis interventions with in-hospital prophylaxis and later placebo or	N=901 Duration varied	Primary: Incidence of DVT, PE or fatal PE within 30 days after surgery, postoperative three month mortality rate Secondary: Symptomatic VTE, bleeding complications, mortality	Primary: No trials reporting on prolonged treatment with UFH, oral anticoagulants or mechanical methods were identified. *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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or no treatment	no treatment			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[71] Thromboprophylaxis (ASA, dextran, heparin [with or without antithrombin III], LMWH [ardeparin*, enoxaparin, tinzaparin], lower extremity PCS or warfarin) vs placebo A prophylactic agent of interest was compared to another method of interest or placebo.	MA (14 trials) Patients receiving prophylaxis for ≥7 days for an elective TKA	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, and all-cause mortality Secondary: Not reported	Primary: For total DVT, all treatments, except dextran and ASA, protected significantly better than placebo (*P*<0.0001). For proximal DVT, no comparison against placebo was available, and rates ranged from 1.7 (ASA) 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 ASA protected better than warfarin (1.7 vs 10.2%; *P*=0.0106). For distal DVT, no comparison against placebo was available. Treatment with LMWH (24.4%) protected significantly better than dextran (71.1%; *P*=0.0001), warfarin (35.6%; *P*=0.0001) and ASA (55.2%; *P*=0.0001). Treatment with warfarin (35.6%) protected significantly better than ASA (55.2%; *P*=0.0045) but worse than SC heparin (21.5%; *P*=0.0029). Treatment with ASA (55.2%) protected significantly less than SC heparin (21.5%; *P*=0.0001) and PCS (29.5%; *P*=0.0051). Rates of symptomatic PE ranged from 0.0 (ASA, PCS 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 (ASA) to 18.9% (SC heparin). No

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				comparison with placebo was available. The rate of minor bleeding ranged from 8.6 (ASA) to 18.3% (SC heparin). Rates of major bleeding ranged from 0.0 (ASA, PCS) 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 (ASA, SC heparin, PCS, placebo, SC heparin/antithrombin III and dextran) to 0.3% (warfarin), but no difference among the treatments were noted. Secondary: Not reported

*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: ARI=absolute relative increase, ARR=absolute relative 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, WMD=weighted mean difference
Miscellaneous abbreviations: ACS=acute coronary syndrome, ASA=aspirin, ALT=alanine transaminase, DTI=direct thrombin inhibitor, DVT=deep vein thrombosis, HIT=heparin induced thrombocytopenia, ICU=intensive care unit, 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, PCS=pneumatic compression stockings, PE=pulmonary embolism, PFS=progression free survival, SCLC=small cell lung cancer, STEMI=ST-segment elevation myocardial infarction, THA=total hip arthroplasty, THR=total hip replacement, TKA=total knee arthroplasty, TKR=total knee replacement, UFH=unfractionated heparin, VKA=vitamin K antagonist, VTE=venous thromboembolism

Special Populations

Table 5. Special Populations[1-4,72,73]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
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.	NA
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.	NA
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	Use caution in patients with a creatinine clearance 30 to 50 mL/minute. Contra-indicated in patients with a creatinine clearance <30 mL/minute.	No dosage adjustment required.	B	Unknown; use with caution.	NA

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
	established.					
Tinzaparin	Tinzaparin may increase the risk for death when administered to elderly patients with renal insufficiency.† Safety and efficacy in children have not been established.	Use with caution in patients with a creatinine clearance ≤50 mL/minute.	Not studied in hepatic impairment.	B	Unknown; use with caution.	Weight-based dosing is appropriate for heavy/ obese patients.

NA=not applicable
*Please see Table 8 for the renal dosing of enoxaparin.
†Compared to unfractionated heparin.

Adverse Drug Events

Table 6. Adverse Drug Events[1-4]

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux	Tinzaparin
Bleeding Reactions				
Anorectal bleeding	-	-	-	✔
Any bleeding reaction	4.4 to 13.6	-	-	-
Cerebral/intracranial bleeding	-	-	-	✔
Epistaxis	-	-	1.3	1.9
Hemarthrosis	-	-	-	✔
Hematemesis	-	-	-	✔
Hematoma	-	-	2.1 to 2.8	≥1
Hematuria	2.9	<1 to 2	-	1
Hemopericardium	-	-	-	✔
Hemoptysis	-	-	-	✔
Hemorrhage	-	5 to 13	-	1.5
Injection site bleeding	-	-	-	✔
Injection site hematoma	0.2 to 7.1	3 to 5	-	≥1
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	-	-	0.0 to 3.5	✔
Rectal bleeding	-	-	-	✔
Reoperation due to bleeding	0.5 to 1.3	-	-	-

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux	Tinzaparin
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	≥1
Angina pectoris	-	-	-	≥1
Back pain	-	-	-	1.5
Bullous eruption	-	-	0.0 to 3.1	≥1
Cellulitis	-	-	-	✔
Cardiac arrhythmia	-	-	-	✔
Chest pain	-	-	-	2.3
Cholestatic hepatitis	-	-	-	✔
Confusion	-	2.2	1.2 to 3.1	≥1
Constipation	-	-	-	1.3
Diarrhea	-	2.2	-	-
Dizziness	-	0.6 to 3.6	-	≥1
Dyspepsia	-	-	-	≥1
Dyspnea	-	3.3	-	1.2
Dysuria	-	-	-	≥1
Ecchymosis	-	<1	-	-
Edema	-	2	-	✔
Elevations in serum transaminases	✔	5.9 to 6.1	0.7 to 2.6	8.8 to 13.0
Epidermal necrolysis	-	-	-	✔
Fever	-	5 to 8	-	1.5
Flatulence	-	-	-	≥1
Gastrointestinal disorder	-	-	-	≥1
Granulocytopenia	-	-	-	✔
Headache	-	-	-	1.7
Healing impaired	-	-	-	≥1
Hypersensitivity	-	-	-	✔
Hypertension	-	-	-	≥1
Hypokalemia	-	-	0.0 to 4.2	-
Hypotension	-	-	0.3 to 3.5	≥1
Infection	-	-	-	≥1
Insomnia	-	-	0.9 to 5.0	≥1
Ischemic necrosis	-	-	-	✔
Local reactions	2 to 13	2	✔	✔
Myocardial infarction/coronary thrombosis	-	-	-	✔
Nausea	-	2.5 to 3.0	-	1.7
Neoplasm	-	-	-	✔
Pain	-	-	-	1.5
Pancytopenia	-	-	-	✔
Peripheral edema	-	<1	-	-
Peripheral ischemia	-	-	-	✔

Adverse Event	Dalteparin	Enoxaparin	Fondaparinux	Tinzaparin
Pneumonia	-	-	-	≥1
Postoperative wound infection	-	-	4.9	-
Priapism	-	-	-	✔
Pruritus	-	-	-	≥1
Pulmonary embolism	-	-	-	2.3
Rash	-	-	-	1.2
Respiratory disorder	-	-	-	≥1
Skin disorder	-	-	-	≥1
Stevens-Johnson syndrome	-	-	-	✔
Tachycardia	-	-	-	≥1
Thrombocythemia	-	-	-	✔
Thrombocytopenia	✔	2.8	✔	0.13 to ≥1.00
Thromboembolism	-	-	-	✔
Thrombophlebitis	-	-	-	≥1
Urinary retention	-	-	-	≥1
Urinary tract infection	-	-	-	3.7
Urticaria	-	-	-	✔
Vomiting	-	-	-	1
Wound drainage increase	-	-	0.6 to 4.5	-

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

Contraindications/Precautions

All of the injectable anticoagulants are contraindicated in patients with major active bleeding.[1-4] In addition, all of the low molecular weight heparin (LMWH) agents should not be used in patients with a known hypersensitivity to the specific medication. Patients who have a hypersensitivity to heparin (dalteparin, enoxaparin and tinzaparin), pork (dalteparin, enoxaparin and tinzaparin), benzyl alcohol (enoxaparin and tinzaparin) and sulfites (tinzaparin) should not be administered these medications. Dalteparin and tinzaparin are also contraindicated in patients with a history of heparin induced thrombocytopenia (HIT) (with or without thrombosis), while enoxaparin is contraindicated in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin.[1,2,4] Patients who are undergoing epidural/neuraxial anesthesia as treatment for unstable angina, being treated for a non-Q-wave myocardial infarction or for prolonged venous thromboembolism (VTE) prophylaxis should not receive dalteparin.[1] Fondaparinux, a factor Xa inhibitor, is contraindicated in patients with severe renal impairment (creatinine clearance, <30 mL/minute), active major bleeding, bacterial endocarditis, thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux and body weight <50 kg (VTE prophylaxis only).[3]

Use of any of the LMWH agents increases the risk of hemorrhage, specifically when used in patients receiving spinal/epidural anesthesia or spinal puncture. The risk increases with the use of post operative indwelling epidural catheters with the concomitant use of additional drugs affecting hemostasis (e.g., nonsteroidal anti-inflammatory drugs), with traumatic or repeated epidural or spinal puncture or in patients with a history of spinal surgery or spinal deformity.[1,2,4] In addition, these agents should be used with caution in conditions with increased risk of hemorrhage as major hemorrhages have been reported.[2,4] In addition, bleeding can occur at any site during therapy with enoxaparin.[2]

HIT can occur during therapy with any of the LMWH agents, and caution should be used when enoxaparin is used in patients with a history of this condition. Thrombocytopenia may also occur in patients receiving enoxaparin or tinzaparin.[2,4]

Multiple-dose vials of dalteparin and enoxaparin contain benzoyl alcohol, which has been associated with a fatal “Gasping Syndrome” in premature infants. Because benzoyl alcohol may cross the placenta,

caution must be exercised when dalteparin or enoxaparin is administered to pregnant women.[1,2] Tinzaparin contains sodium metabisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening asthmatic episodes in susceptible patients.[4]

The individual LMWH agents cannot be used interchangeably (unit for unit) with heparin or other LMWH agents. The reason is because these agents all differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units and dosage. Each of these agents has its own instruction for use.[2,4]

Periodic complete blood counts are recommended during the course of treatment with any of the LMWH agents. In addition, anti-factor Xa may be used to monitor the anticoagulant effect of these medications.[1,2,4]

Enoxaparin and tinzaparin should be used with care in patients with bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic neuropathy, renal dysfunction and hemorrhage.[2,4]

To minimize the risk of bleeding following percutaneous coronary revascularization procedures in patients receiving enoxaparin, precise adherence to the intervals recommended between doses should be exercised. The use of enoxaparin for thromboprophylaxis in pregnant women with mechanical heart valves has not been adequately evaluated. These patients may be at a higher risk for thromboembolism and have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery.[2]

Tinzaparin may increase the risk of death, compared to unfractionated heparin, when administered to elderly patients with renal insufficiency. Priapism has also been reported from post-marketing surveillance as a rare occurrence; however, in some cases surgical intervention was required.[4]

Fondaparinux has the same precautions associated with its use as the LMWH agents in terms of hemorrhages, and the medication should be used with caution in conditions with increased risk of hemorrhage. Agents that increase the risk of hemorrhage should not be administered with fondaparinux, unless essential for the management of the underlying condition. Fondaparinux should not be administered earlier than six to eight hours after surgery; administration earlier than this time increases the risk of major bleeding. In addition, fondaparinux increases the risk of bleeding in patients with impaired renal function due to reduced clearance; therefore, caution should be exercised when used in patients with a creatinine clearance of 30 to 50 mL/minute. Renal function should periodically be assessed throughout therapy, and if a patient develops severe renal impairment the medication should be discontinued. Fondaparinux also increases the risk of bleeding in patients who weigh <50 kg; therefore, the medication should not be administered as prophylactic therapy for patients undergoing hip fracture, hip replacement or knee replacement surgery or abdominal surgery who weigh <50 kg. The medication should also be used with caution for the treatment of pulmonary embolism and deep vein thrombosis. Similar to the LMWH agents, thrombocytopenia can occur with the administration of fondaparinux. Finally, the packaging of the prefilled syringe of fondaparinux contains dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.[3]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for Fragmin® (dalteparin), Lovenox® (enoxaparin), Innohep® (tinzaparin)[74]

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

WARNING
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)[74]

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 versus 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.

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.[1-4]

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 7. Drug Interactions[74]

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, reduce the daily dose 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]

All patients receiving tinzaparin should be evaluated for bleeding disorders before initiating therapy. Again, since coagulation parameters are unsuitable for monitoring tinzaparin activity, routine monitoring of coagulation parameters is not required.[4]

Table 8. Dosing and Administration[1-4]

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 2 through 6; 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, 5 to 8 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 starting 1 to 2 hours prior to surgery; postoperatively, 2,500 IU SC QD (usual duration, 5 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 QD postoperatively (usual duration, 5 to 10 days). Alternatively, patients with malignancy, can administer 2,500 IU SC 1 to 2 hours prior to surgery, followed by 2,500 IU SC 12 hours later, then 5,000 IU SC QD (usual duration, 5 to 10 days). Prophylaxis of DVT in patients undergoing hip replacement surgery:	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
	Injection: preoperatively, 5,000 IU SC 10 to 14 hours before surgery and 2,500 IU SC within 2 hours before surgery; postoperatively, 2,500 to 5,000 IU SC 4 to 8 hours after surgery and 5,000 IU SC QD (usual duration, 5 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 2 days and continued until clinical stabilization (usual duration, 7 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, 6 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 2 hours prior to surgery; postoperatively, 40 mg SC QD (usual duration, 7 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: preoperatively, 30 mg SC 12 to 24 hours prior to surgery; postoperatively, 40 mg SC QD for 3 weeks (usual duration, 7 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: preoperatively, 30 mg SC 12 to 24 hours prior to surgery or 40 mg SC 12(±3) hours prior to surgery; postoperatively, 30 mg SC BID or 40 mg SC QD Injection (patients with creatinine clearance <30 mL/minute): 30 mg SC QD	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
	Treatment of acute DVT: Injection (outpatient): 1 mg/kg SC every 12 hours for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (average duration, 7 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 5 days and until a therapeutic oral anticoagulant effect has been achieved (average duration, 7 days)[¶] Injection (inpatients with creatinine clearance <30 mL/minute): 1 mg/kg SC QD Treatment of acute ST-segment elevation myocardial infarction: Injection: initial, 1 mg/kg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC BID; maximum, 100 mg for the first 2 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 6 to 8 hours after surgery (usual duration, 5 to 9 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 6 to 8 hours after surgery (usual duration, 5 to 9 days)[§§] An extended prophylaxis course of up to 24 additional days is recommended.[‖‖] Prophylaxis of DVT in patients undergoing hip replacement surgery:	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
	Injection: 2.5 mg SC QD after hemostasis has been established, initiated no earlier than 6 to 8 hours after surgery (usual duration, 5 to 9 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 6 to 8 hours after surgery (usual duration, 5 to 9 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, 5 to 9 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, 5 to 9 days)[¶¶]		
Tinzaparin	Treatment of acute DVT: Injection: 175 IU/kg SC QD for ≥6 days and until the patient is adequately anticoagulated with warfarin	Safety and efficacy in children have not been established.	Injection: 20,000 IU/mL (2 mL)[††]

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 5 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 17 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.
††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.
¶¶A total of 26 days of treatment have been administered in clinical trials.

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of 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 guideline summaries focus on the role of the injectable anticoagulants in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Chest Physicians:	Parenteral anticoagulants • Monitoring antithrombotic effect:

Clinical Guideline	Recommendations
Antithrombotic and Thrombolytic Therapy 8th Edition (2008)[8]	o In patients treated with low molecular weight heparin (LMWH), routine coagulation monitoring is not recommended. o In pregnant women treated with therapeutic doses of LMWH, monitoring of anti-Xa levels is recommended. • Dosing and monitoring in special situations: o In obese patients receiving LMWH, weight-based dosing is suggested. o In patients with severe renal insufficiency (creatinine clearance <30 mL/minute) who require therapeutic anticoagulation, the use of unfractionated heparin (UFH) instead of LMWH is suggested. If LMWH is used in these patients, use of 50% of the recommended dose is suggested. <u>Prevention of venous thromboembolism (VTE)</u> • General recommendations: o It is recommended that renal function be considered when making decisions about the use and/or dose of LMWH, fondaparinux and other antithrombotic drugs that are cleared by the kidneys. Depending on the circumstances, it is recommended to avoid the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent or monitoring the drug level or its anticoagulant effect. • Orthopedic surgery-elective hip replacement: o The routine use of one of the following anticoagulant options is recommended: LMWH, fondaparinux or adjusted-dose vitamin K antagonist (VKA). o Use of any of the following as the sole method of thromboprophylaxis is not recommended: aspirin (ASA), dextran, low dose unfractionated heparin (LDUH), graduated compression stockings or venous foot pump. • Orthopedic surgery-elective knee replacement: o Routine thromboprophylaxis using LMWH, fondaparinux or adjusted-dose VKA is recommended. o The optimal use of intermittent pneumatic compression is an alternative option to anticoagulant thromboprophylaxis. o Use of any of the following as the only method of thromboprophylaxis is not recommended: ASA, LDUH or venous foot pump. • Orthopedic surgery-knee arthroscopy: o In patients who do not have additional thromboembolic risk factors, it is suggested that clinicians not routinely use thromboprophylaxis other than early mobilization. o In patients who have additional thromboembolic risk factors or who have undergone a complicated surgery, LMWH is recommended for thromboprophylaxis. • Orthopedic surgery-hip fracture surgery: o Routine thromboprophylaxis with fondaparinux, LMWH, adjusted-dose VKA or LDUH is recommended. o Use of ASA alone is not recommended. o In patients who will likely have a delayed surgery,

Clinical Guideline	Recommendations
	thromboprophylaxis with LMWH or LDUH initiated during the time between hospital admission and surgery is recommended. • Other thromboprophylaxis issues in major orthopedic surgery: o For patients receiving LMWH, starting therapy either preoperatively or postoperatively is recommended. o For patients receiving fondaparinux, starting therapy either six to eight hours after surgery or the next day is recommended. o For patients undergoing total hip replacement, total knee replacement or hip fracture surgery, thromboprophylaxis for at least 10 days is recommended. o For patients undergoing total hip replacement, it is recommended that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery. Recommended options for extended prophylaxis include LMWH, a VKA or fondaparinux. o For patients undergoing total knee replacement, it is suggested that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery. Recommended options for extended prophylaxis include LMWH, a VKA or fondaparinux. o For patients undergoing hip fracture surgery, it is recommended that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery. Recommended options for extended prophylaxis include fondaparinux, LMWH or a VKA. <u>Medical conditions</u> • For acutely ill medical patients admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease or inflammatory bowel disease, thromboprophylaxis with LMWH, LDUH or fondaparinux is recommended. • For medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant thromboprophylaxis, the optimal use of mechanical thromboprophylaxis is recommended. <u>Cancer patients</u> • In patients undergoing surgical procedures, routine thromboprophylaxis that is appropriate for the type of surgery is recommended. • In patients who are bedridden with an acute medical illness, routine thromboprophylaxis as for other high risk medical patients is recommended. • In patients with indwelling central venous catheters, use of prophylactic doses of LMWH or mini doses of warfarin to prevent catheter-related thrombosis is not recommended. • In patients receiving chemotherapy or hormonal therapy, the routine use of thromboprophylaxis for the primary prevention of VTE is not recommended. • The routine use of primary thromboprophylaxis to try to improve

Clinical Guideline	Recommendations
	survival is not recommended. Antithrombotic therapy for venous thromboembolic disease • Initial anticoagulation of acute deep vein thrombosis (DVT) of the leg: o For patients with objectively confirmed DVT, short-term treatment with subcutaneous (SC) LMWH, intravenous (IV) UFH, monitored SC UFH, fixed-dose SC UFH or SC fondaparinux rather than no such acute treatment is recommended. o For patients with a high clinical suspicion of DVT, treatment with anticoagulants while awaiting the outcome of the diagnostic tests is recommended. o In patients with acute DVT, initial treatment with LMWH, UFH or fondaparinux for at least five days, until the International normalized Ratio (INR) is ≥2.0 for 24 hours, is recommended. o In patients with acute DVT, initiation of VKA together with LMWH, UFH or fondaparinux on the first treatment is recommended. • Duration of anticoagulant therapy: o For patients with DVT secondary to a transient (reversible) risk factor, three months of VKA therapy is recommended over shorter treatment periods. o For patients with unprovoked DVT, at least three months of VKA therapy is recommended. After three months, all patients should be evaluated for the risk-benefit ratio of long term therapy. For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long term treatment is recommended. For patients with a second episode of unprovoked VTE, long term treatment is recommended. For patients with a first isolated distal DVT that is unprovoked, three months of anticoagulant therapy is sufficient rather than indefinite therapy. o For patients with DVT and cancer, LMWH for the first three to six months of long term anticoagulant therapy is recommended. For these patients, subsequent therapy with VKA or LMWH indefinitely or until the cancer is resolved is recommended. o In patients who receive long term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed periodically. • Intensity of anticoagulant effect: o In patients with DVT, it is recommended that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 to 3.0) for all treatment durations. o For patients with unprovoked DVT who have a strong preference for less frequent INR testing, after the first three months of conventional intensity anticoagulation, low intensity therapy (INR range, 1.5 to 1.9) with less frequent monitoring over stopping therapy is suggested.

Clinical Guideline	Recommendations
	o High intensity VKA therapy (INR range, 3.1 to 4.0) compared to an INR range of 2.0 to 3.0 is not recommended. • Treatment of asymptomatic DVT of the leg: o In patients who are unexpectedly found to have asymptomatic DVT, the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT is recommended. • IV or SC UFH, SC LMWH, SC fondaparinux and VKA for the initial treatment of pulmonary embolism (PE): o For patients with objectively confirmed PE, short term treatment with SC LMWH, IV UFH, monitored SC UFH, fixed dose SC UFH or SC fondaparinux rather than no such acute treatment is recommended. Patients with acute PE should also be routinely assessed for treatment with thrombolytic therapy. o For patients in whom there is a high clinical suspicion of PE, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended. o In patients with acute PE, initial treatment with LMWH, UFH or fondaparinux for at least five days and until the INR is ≥2.0 for at least 24 hours is recommended. o In patients with acute PE, initiation of VKA together with LMWH, UFH or fondaparinux on the first day of treatment is recommended. o In patients with acute nonmassive PE, initial treatment with LMWH over IV UFH is recommended. In patients with massive PE, in other situations where there is concern about SC absorption or in patients in whom thrombolytic therapy is being considered or planned, IV UFH over SC LMWH, SC fondaparinux or SC UFH is suggested. o In patients with acute PE treated with LMWH, routine monitoring with anti-factor Xa level measurements is not recommended. o In patients with acute PE and severe renal failure, UFH over LMWH is suggested. <u>Long term treatment of acute PE</u> • For patients with secondary PE to a transient risk factor, three months of VKA therapy over shorter treatment periods is recommended. • For patients with unprovoked PE, at least three months of VKA therapy is recommended. After three months, all patients should be evaluated for the risk-benefit ratio of long term therapy. For patients with a first unprovoked VTE that is a PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long term treatment is recommended. For patients with a second episode of unprovoked VTE, long term treatment is recommended. • For patients with PE and cancer, LMWH for the first three to six months of long term anticoagulant therapy is recommended. For these patients, subsequent therapy with VKA or LMWH indefinitely or until the cancer is resolved is recommended.

Clinical Guideline	Recommendations

	• In patients who receive long term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed periodically.
	• In patients with PE, it is recommended that the dose of VKA be adjusted to maintain a target INR of 2.5 (range, 2.0 to 3.0) for all treatment durations.
	• For patients with unprovoked PE who have a strong preference for less frequent INR testing, after the first three months of conventional-intensity anticoagulation, low intensity therapy (INR range, 1.5 to 1.9) with less frequent monitoring over stopping therapy is suggested.
	• High intensity VKA therapy (INR range, 3.1 to 4.0) compared to an INR range of 2.0 to 3.0 is not recommended.
	• In patients who are unexpectedly found to have asymptomatic PE, the same initial and long-term anticoagulation as for comparable patients with symptomatic PE is recommended.
	
	<u>Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes (NSTE ACS)-anticoagulant therapies</u>
	• Anticoagulation with UFH, LMWH, bivalirudin or fondaparinux over no anticoagulation is recommended.
	  o Routine monitoring of the anticoagulant effect of LMWH is not recommended. Careful attention is needed to appropriately adjust LMWH dose in patients with renal insufficiency.
	• For NSTE ACS patients who will undergo an early invasive strategy of management (i.e., diagnostic catheterization followed by anatomy-driven revascularization):
	  o UFH (with a glycoprotein [GP] IIb/IIIa inhibitor) over either LMWH or fondaparinux is recommended.
	• For NSTE ACS patients in whom an early conservative or delayed invasive strategy of management is to be used:
	  o Fondaparinux over enoxaparin is recommended.
	  o LMWH over UFH is recommended. Continuing LMWH during percutaneous intervention (PCI) treatment of patients with NSTE ACS when LMWH has been started as the upstream anticoagulant is recommended.
	• In low to moderate risk patients with NSTE ACS undergoing PCI, bivalirudin or UFH, both in combination with a GP IIb/IIIa inhibitor, over alternative antithrombotic regimens is recommended.
	
	<u>Acute ST-segment elevation myocardial infarction (STEMI)-antiplatelet/antithrombotic therapy</u>
	• LMWH:
	  o Regardless of whether or not reperfusion therapy is utilized, reviparin (not available in the United States) over no therapy is recommended. For patients undergoing primary PCI, UFH should be used periprocedurally and reviparin initiated one hour after sheath removal.
	  o In patients receiving fibrinolytic therapy who have preserved renal function, enoxaparin for up to eight days over UFH is recommended.

Clinical Guideline	Recommendations
	• Fondaparinux: o In patients not receiving reperfusion therapy, fondaparinux over no therapy is recommended. o In patients receiving fibrinolytic therapy and thought not to have an indication for anticoagulation, fondaparinux over no therapy is recommended. o In patients receiving fibrinolytic therapy and thought to have an indication for anticoagulation, fondaparinux could be used as an alternative to UFH. o In patients undergoing primary PCI, fondaparinux is not recommended.
American College of Cardiology/American Heart Association: **American College of Cardiology/American Heart Association 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction (2007)**[9]	<u>Recommendations for antiplatelet/anticoagulant therapy in patients for whom diagnosis of unstable angina/NSTEMI 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. Limited data are available for the use of other LMWHs. o Enoxaparin or fondaparinux are preferred over UFH, unless coronary artery bypass grafting (CABG) surgery is planned within 24 hours. • Additional considerations: o For patients in whom CABG is selected as a postangiography management strategy, anticoagulation therapy should be managed as follows: ▪ Discontinue enoxaparin 12 to 24 hours before CABG and dose with UFH per institutional practice. ▪ Discontinue fondaparinux 24 hours before CABG and dose with UFH per institutional practice. o For patients in whom PCI has been selected as a postangiography management strategy, anticoagulant therapy should be discontinued after PCI for uncomplicated cases. o For patients in whom medical therapy is selected as a postangiography management strategy and in whom no significant obstructive coronary artery disease (CAD) on angiography was found, anticoagulation therapy should be administered at the discretion of the clinician. If CAD was found, anticoagulation therapy should be managed as follows: ▪ Continue enoxaparin or fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic angiography.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary**	• Anticoagulation is recommended for all patients in addition to antiplatelet therapy. • Anticoagulation should be selected according to the risk of both ischemic and bleeding events. • Several anticoagulants are available including UFH, LMWH, fondaparinux and bivalirudin. The choice depends on the initial

Clinical Guideline	Recommendations
Syndromes (2007)[10]	strategy. • In an urgent invasive strategy UFH, enoxaparin or bivalirudin should be immediately started. • In a non-urgent situation, as long as a decision between an early invasive or conservative strategy is pending: o Fondaparinux is recommended on the basis of the most favorable efficacy and safety profiles. o Enoxaparin should only be used if the bleeding risk is low because it has less favorable safety and efficacy profiles compared to fondaparinux. o Because the efficacy and safety profiles of other LMWHs (other than enoxaparin) or UFH relative to fondaparinux is unknown, these agents cannot be recommended over fondaparinux. o At PCI procedures, the initial anticoagulant should also be maintained during the procedure regardless of whether this treatment is UFH, enoxaparin or bivalirudin, whereas additional UFH in standard dose is necessary in the case of fondaparinux. o Anticoagulation can be stopped within 24 hours after an invasive procedure. In a conservative strategy, fondaparinux, enoxaparin or other LMWH may be maintained up to hospital discharge.
American College of Cardiology/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 Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update) (2009)**[11,12]	<u>Recommendations for the use of parenteral anticoagulants (2009 focused update):</u> • For patients undergoing PCI 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. <u>Initial recognition and management in the emergency department-LMWH as ancillary therapy to reperfusion therapy:</u> • LMWH might be considered an acceptable alternative to UFH as ancillary therapy for patients <75 years of age who are receiving 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 STEMI who are at high risk for systemic emboli (e.g., large or anterior myocardial

Clinical Guideline	Recommendations
	infarction, atrial fibrillation, previous embolus, known left ventricular thrombus, cardiogenic shock). • It's reasonable that STEMI 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 ASA use and early mobilization. Other complications: • STEMI 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 ASA). 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 STEMI 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 STEMI 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.

Conclusions

The injectable anticoagulants include low molecular weight heparin (LMWH) agents (dalteparin [Fragmin®], enoxaparin [Lovenox®], tinzaparin [Innohep®]) and factor Xa inhibitors (fondaparinux [Arixtra®]). Both classes of agents work by binding to antithrombin, causing inhibition of the clotting factors thrombin and factor Xa.[1-4] Of note, these agents have much more inhibitory effect on factor Xa than thrombin.[5,6] Also, because the LMWH agents are prepared using different methods of depolymerization, the various agents differ and are not clinically interchangeable.[6] Currently, enoxaparin is the only injectable anticoagulant that is available generically.[7]

In general, the injectable anticoagulants are Food and Drug Administration (FDA) approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Some of the 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 treatment and/or thromboprophylaxis of VTE may be appropriate depending on the specific clinical situation.[8] The evidence from clinical trials and the recommendations from clinical guidelines support the use of the injectable anticoagulants in their FDA approved indications.[8-12,14-71] Several placebo-controlled trials have consistently demonstrated the efficacy of the injectable anticoagulants, but when compared to other methods of anticoagulation (e.g., heparin, unfractionated heparin, warfarin), their "superiority" in terms of recurrent VTE and safety is not always demonstrated.[23-28,31-46,48,60, 63-71] The data from these clinical 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.[49-54] However, data from two clinical trials revealed no significant difference between treatment with fondaparinux compared to dalteparin or enoxaparin in the development of VTE.[49,53] Additionally, there again is generally no distinction made between the use of LMWH agents and fondaparinux within the guidelines for VTE prophylaxis and/or treatment as both therapies are recommended as potential appropriate options.[8]

According to the American College of Chest Physicians, routine use of a LMWH agent, fondaparinux or a vitamin K antagonist (VKA) for VTE thromboprophylaxis is recommended in patients undergoing an orthopedic surgery. In acutely ill medical patients and in cancer patients, LMWH agents, low dose unfractionated heparin or fondaparinux, and LMWH agents or a VKA respectively, are recommended for VTE thromboprophylaxis. In these situations, thromboprophylaxis with an injectable anticoagulant typically lasts for at least five days; however, extended therapy (up to 35 days) may be required in some patients. Anticoagulation for the treatment of an acute deep vein thrombosis should be initiated with a LMWH agent, unfractionated heparin or fondaparinux. In addition, a VKA, together with one of these agents, should be initiated on the first day of treatment. Recommendations for the initial treatment of an acute pulmonary embolism are the same. Anticoagulation with an injectable anticoagulant will typically last for at least five days; however, again in some patients extended prophylaxis may be warranted, especially in cancer patients.[8]

Appendix I: Utilization Within This Drug Class for DVHA: October 1, 2010 to March 31, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost $	Avg $/Rx
Lovenox®	201	327	90.83%	$386,499.92	$1,181.96
Arixtra®	6	22	6.11%	$42,617.44	$1,937.16
Fragmin®	8	10	2.78%	$22,341.86	$2,234.19
Enoxaparin	1	1	0.28%	$302.64	$302.64
Class Total:	**----**	**360**	**100%**	**$451,761.86**	**$1,254.89**

Recommendations

In recognition of the well established role of the injectable anticoagulants for prophylaxis and/or treatment of venous thromboembolism and in the management of acute coronary syndromes and ST-segment elevation myocardial infarction, their generally equivalent safety and efficacy in the management of these disease states, and the lack of distinction among the various agents within guidelines in terms of a preferred agent, no changes to the current Department of Vermont Health Access (DVHA) approval criteria (below) are recommended.

Enoxaparin

- The patient has a documented intolerance to brand Lovenox®.

Innohep®

- The diagnosis is treatment of acute, symptomatic deep vein thrombosis (DVT) with or without pulmonary embolism, administered in conjunction with warfarin sodium.

AND

- The patient does not have a bleeding disorder or documented heparin-induced thrombocytopenia (HIT).

AND

- The prescriber must provide a clinically valid reason why one of Lovenox®, Fragmin® or Arixtra® cannot be used.

OR

- The patient has been started and stabilized on the requested medication in conjunction with warfarin.

At this time, Fragmin®, Lovenox® and Arixtra® are preferred agents on the DVHA preferred drug list (PDL) and do not require prior authorization.

References

1. Fragmin® [package insert]. New York (NY): Pfizer Inc; 2010 Oct.
2. Lovenox® [package insert]. Greenville (NC): Sanofi-aventis U.S. LLC; 2009 Dec.
3. Arixtra® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2010 Mar.
4. Innohep® [package insert]. Parsippany (NJ): LEO Pharma Inc.; 2010 May.
5. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98.
6. 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-159S.
7. FDA approves first generic enoxaparin sodium injection [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2010 Jul 23 [cited 2011 Mar]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm.
8. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;133:71S-109S.
9. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Col Cardiol. 2007;50(7):e7-e157.
10. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology. Eur Heart J. 2007;28:1598-660.
11. 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.
12. 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.
13. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2011 Feb]. Available from: http://www.thomsonhc.com/.
14. 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.
15. 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 with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28:2077-86.
16. Magee K, Sevcik WW, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. Cochrane Database of Systematic Reviews. 2003, Issue 1. Art. No.:CD002132. DOI:10.1002/14651858.CD002132.
17. 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.
18. 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.
19. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53.

20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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 versus placebo. Lancet. 1996;348:224-8.

37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Ann Surg. 2001;233(3):438-44.
44. 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.
45. 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.
46. 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.
47. Simonneau G, Laporte S, Mismetti P, Derlon A, Samii K, Samama SM, et al. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. J Thromb Haemost. 2006;4:1693-700.
48. 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.
49. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212-20.
50. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715-20.
51. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-10.
52. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-304.
53. Turpie AFF, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet. 2002;359:1721-6.
54. 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.

55. Eikelboom JW, Quinlan DJ, O'Donnell M. Major bleeding, mortality and efficacy of fondaparinux in venous thromboembolism prevention trials. Circulation. 2009;120;2006-11.
56. Jorgensen PS, Warming T, Hansen K, Paltved C, Berg HV, Jensen R, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast. A venografic controlled study. Thromb Res. 2002;105:477-80.
57. Romera A, Cairols MA, Vila-Coll R, Marti X, Colome E, Bonell A, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg. 2009;37:349-56.
58. Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J. Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. Am J Obstet Gynecol. 2004;190:495-501.
59. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridies P, Nikolaou A, Dimitroulis D, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. Eur J Vasc Endovasc Surg. 2005;29:638-50.
60. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119:1062-72.
61. 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.
62. van Dongen CJ, Mac Gillavry MR, Prins MH. Once versus 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.
63. 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.
64. 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.
65. Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors versus 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.
66. Erkens PMG, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database of Systematic Reviews. 2010, Issue 9. Art. No.:CD001100. DOI:10.1002/14651858.CD001100.pub3.
67. Othieno R, Abu Affan M, Okpo E. Home versus in-patient treatment for deep vein thrombosis. Cochrane Database of Systematic Reviews. 2007, Issue 3. Art. No.:CD003076. DOI:10.10002/14651858.CD003076.pub2.
68. 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.
69. 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.
70. 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.
71. 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.
72. Fondaparinux: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2010 [cited 2011 Mar]. Available from: http://www.utdol.com/utd/index.do.
73. Tinzaparin: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2010 [cited 2011 Mar]. Available from: http://www.utdol.com/utd/index.do.

74. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2010 [cited 2011 Mar]. Available from: http://online.factsandcomparisons.com.