

New Treatment Options for Acute Coronary Syndromes

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Abstract

Complications from atherosclerotic coronary artery disease are the principal cause of death worldwide. Many therapeutic strategies have been developed to reduce the burden of this disease. Systemic antithrombotic therapy, typically with unfractionated heparin, has long been a mainstay in the management of acute coronary syndromes (ACS) despite several limitations, including intravenous administration and unpredictable pharmacokinetics necessitating frequent monitoring. In recent years, newer agents without these limitations have been developed and evaluated in clinical trials. This review focuses on novel antithrombotic therapies for ACS, particularly fondaparinux sodium, a synthetic inhibitor of clotting factor Xa.

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Atherosclerotic coronary artery disease (CAD) continues to pose an enormous burden worldwide and is the principal cause of death in the developed world. It is estimated that in the United States alone, more than 700 000 individuals will have a new coronary attack, and about 500 000 will have a recurrent attack in the year 2006.¹

Acute coronary syndromes (ACS), which include unstable angina (UA) and myocardial infarction (MI) with (STEMI) or without (NSTEMI) ST-segment elevation, present a unique challenge to clinicians because of the high rate of mortality and morbidity associated with these conditions. Recent statistics by the American Heart Association (AHA) indicate that approximately 25% of men and 38% of women will die within 1 year of having an initial recognized MI, and people who survive the acute stage have an increased risk of illness and death that is up to 15 times higher than that of the general population.^{1,2} The economic impact of ACS is also very high, costing Americans more than

\$400 billion this year, according to AHA estimates.¹

The treatment of ACS typically includes the use of antithrombotic agents, along with several other classes of medication. When using antithrombotic therapy, however, providers have always had to perform a careful “balancing act” between efficacy and reduction in ischemic events with increased risk of bleeding because reducing the probability of thrombotic events has meant an unavoidable increase in the risk of bleeding complications.³ However, some recent trials indicate that with the use of a new type of anticoagulant, it may now be possible to prevent thrombosis without a significant increase in the risk of bleeding.^{4,5}

Thrombotic Cascade

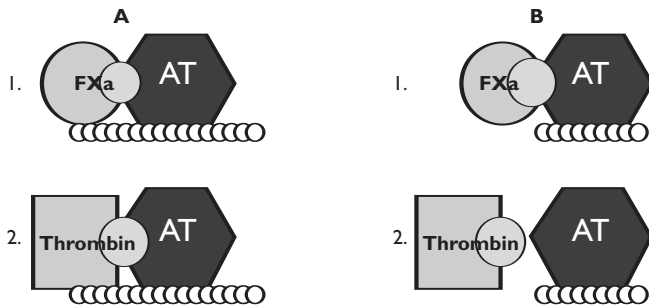
Our understanding of the pathophysiology of CAD has evolved significantly in the past few years, and it is now thought that atherosclerosis represents a chronic inflammatory response to the deposition and modification of lipids within large- and medium-sized arteries throughout the vasculature.⁶ ACS arise after the rupture of an inflamed atherosclerotic plaque, exposing prothrombotic contents of the vascular matrix to the blood.

After plaque rupture, circulating platelets adhere to, and are activated by, the exposed components of the vascular matrix. Tissue factor is also exposed to plasma after plaque rupture, initiating the thrombotic cascade via its interaction with coagulation factor VII. Activated factor VII (factor VIIa) molecules activate small amounts of factor X that

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Figure 1. Differences in Inhibitory Mechanisms Between UFH and Shorter-chain Heparinoids (LMWH and Fondaparinux)



(A-1) UFH binds to ATIII (AT) and induces a conformational change allowing binding of factor Xa (FXa) and thrombin. (A-2) Thrombin binding requires further binding to heparin to bring the molecules into close proximity. (B-1) LMWH and fondaparinux bind the active site of ATIII, but (B-2) are of insufficient size to bind thrombin, and thus derive efficacy solely from the interaction with FXa.

UFH indicates unfractionated heparin; LMWH, low molecular weight heparins; ATIII, antithrombin III.

Source: Adapted with permission from Reference 8.

combine with factor Va to produce thrombin (factor IIa). Thrombin then serves to amplify the response to the injury by further activation of platelets.

These interactions result in the assembly of the prothrombinase complex on the surface of activated platelets and the generation of large amounts of thrombin that catalyze the production of fibrin and cause the clinical manifestations of thrombosis and ACS.⁷ Thrombin generation is downregulated via a variety of mechanisms, most notably the serine protease inhibitor antithrombin III (ATIII), which inactivates circulating coagulation factors, including factor Xa and thrombin.⁸

Current Antithrombotic Therapy

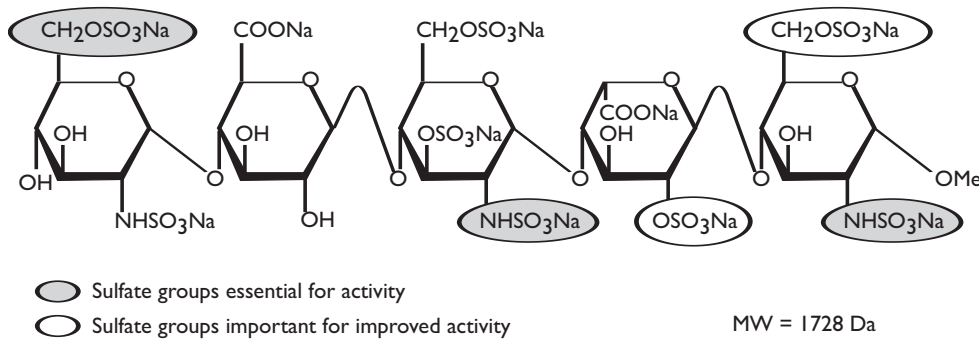
Unfractionated heparin (UFH). In addition to other standard therapies, such as nitrates, antiplatelet agents, beta blockers, and angiotensin-converting enzyme inhibitors, aldosterone antagonists and antithrombotic drugs have been a mainstay of short-term therapy for ACS for many years. Despite limited published evidence, UFH continues to be widely used as the initial anticoagulant for most ACS.⁹ UFH is a heterogeneous mixture of linear polysaccharides that activates ATIII, dramatically

enhancing its ability to inhibit thrombin and factor Xa. The heparin and ATIII interaction occurs via a specific pentasaccharide sequence (present on only 30%-50% of the UFH molecules) that induces a conformational change in ATIII. Thrombin (factor IIa) inhibition requires a subsequent nonspecific interaction with the residual heparin molecule to bring the inhibitor and the clotting factor into close proximity. A covalent interaction between factor IIa and ATIII then inhibits thrombin and allows heparin to dissociate (Figure 1). Inactivation of factor Xa, on the other hand, is less dependent on the nonspecific “bridging” interaction to facilitate the interaction with ATIII, and is about 10 times less sensitive to UFH than thrombin.^{8,10}

The clinical evidence supporting the use of UFH in the setting of ACS is far from definitive. Trials comparing UFH with a placebo or aspirin alone in NSTEMI have produced mixed results.¹⁰ There is, however, some direct evidence supporting the use of UFH in combination with aspirin in ACS. In a meta-analysis of 6 randomized trials (n = 1353) in which the combination of UFH and aspirin was compared with aspirin alone, UFH was found to provide a 33% relative reduction in the risk of cardiovascular death and recurrent MI (relative risk [RR] = 0.67; 95% confidence interval [CI], 0.44-1.02).¹¹

With regard to STEMI, there is no clear consensus regarding the role of UFH, despite more than 40 years of experience with the drug.⁹ When an invasive approach involving immediate cardiac catheterization and intervention is planned, the use of UFH is warranted. Among patients treated with fibrinolytics, however, recommendations for anticoagulation tend to be based on expert opinion rather than clinical evidence. Administration of UFH is generally recommended with fibrin-specific agents or when patients are at high risk for thromboembolic complications, and coadministration with streptokinase is said to be “reasonable.”⁹

UFH is typically administered intravenously in the setting of ACS. Because of adherence to plasma proteins and cell surfaces, as well as complex clearance pharmacokinetics, there is significant variability in the bioavailability of and response to UFH,

Figure 2. Molecular Structure of Fondaparinux

MW indicates molecular weight.

Source: Reprinted with permission from Reference 10.

mandating frequent monitoring of activated partial thromboplastin time.¹² Furthermore, approximately 1% of patients treated with UFH for 5 or more days will develop heparin-induced thrombocytopenia (HIT), leaving them at significant relative (odds ratio, 20-30) and absolute risk (30%-75%) for thrombotic complications.^{13,14} HIT arises as a result of an interaction between UFH and platelet factor 4 (PF4), which increases thrombin production and may lead to thrombosis.¹⁴

Another complication with the use of UFH is bleeding. In the trials that established UFH as an adjunct to aspirin in ACS, meta-analysis reveals a small, nonsignificant increase in major bleeding (RR = 1.88, 95% CI, 0.60-5.87; $P = .28$).^{11,15} It should be noted, however, that these trials were performed before the widespread use of invasive procedures, and the associated periprocedural bleeding, in ACS.

Low molecular weight heparins (LMWH). LMWH, produced by depolymerizing UFH, are more homogeneous molecules, approximately one third of which possess an ATIII binding pentasaccharide sequence. The smaller size of LMWH makes these molecules less able to form a bridge between ATIII and factor IIa, therefore the clinical effects are more dependent on the anti-factor Xa properties of these drugs (Figure 1). These smaller molecules exhibit less adhesion to plasma proteins and cell surfaces,

hence they have more reliable pharmacokinetics. Additionally, they are less likely to form immune complexes with PF4 and to cause HIT.

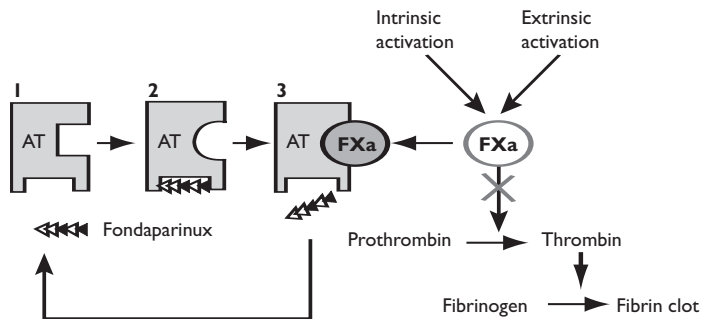
Since the introduction of these drugs, several trials have suggested that they are somewhat more efficacious with similar rates of significant bleeding when compared with UFH in the setting of high-risk ACS.¹² LMWH have also gained popularity because they are administered subcutaneously and, in most cases, require no monitoring.^{16,17} It should be noted, however, that LMWH must be used with caution in patients with renal dysfunction and that, unlike UFH, there is no reversal agent. Additionally, although less common, treatment with LMWH is also associated with HIT.^{13,14}

Factor Xa Inhibition: Fondaparinux Sodium

Discovering the exact mechanism of action of the heparinoids led to the development of compounds that inhibit factor Xa in the coagulation cascade.¹⁸ Among these novel compounds, fondaparinux sodium has been particularly promising, having been shown to be safe, efficacious, and cost-effective in a number of clinical scenarios, including the treatment and prophylaxis of deep vein thrombosis and pulmonary embolism.¹⁹⁻²²

Fondaparinux is a synthetic pentasaccharide (Figure 2) that binds ATIII, resulting in a 340-fold increase in the rate of factor Xa inhibition over the basal rate (Figure 3).^{8,23}

Figure 3. Fondaparinux Mechanism of Action



Fondaparinux activates antithrombin III (AT), increasing affinity for factor Xa (FXa) 340-fold. Activated FXa inhibits the “intrinsic” and “extrinsic” arms of the coagulation cascade, indirectly causing a reduction in thrombin generation.

Source: Reprinted with permission from Reference 10.

The compound is administered subcutaneously and is rapidly absorbed, with linear pharmacokinetics providing effective anticoagulation with once-daily dosing and no apparent need for monitoring. It is excreted unchanged in the urine and must be dose-adjusted in patients with renal dysfunction. Fondaparinux does not bind significantly to other plasma proteins or produce the high-affinity immunoglobulins that are responsible for HIT.⁸ Although fondaparinux would theoretically appear to be a good choice for the treatment of HIT, there are, as of yet, limited data regarding its use in this setting.^{13,14}

OASIS-5: Fondaparinux Versus Enoxaparin in NSTEMI or UA

Two large clinical trials have been published recently in which fondaparinux was evaluated in the setting of ACS. In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial,⁴ 20 078 patients admitted with ACS were treated with either fondaparinux or enoxaparin, an LMWH.

Patients presenting within 24 hours of symptom onset who had serologic evidence of MI or electrocardiographic evidence of ischemia were eligible for enrollment. Exclusion criteria included STEMI, contraindications to antithrombotic therapy, or serum creatinine levels of ≥ 3.0 mg/dL. Patients were treated with 2.5 mg of fonda-

parinux daily or with 1 mg/kg of enoxaparin twice daily. Fondaparinux was administered until hospital discharge or for 8 days (whichever occurred first), whereas enoxaparin was administered for 2 to 8 days or until the patient was in a clinically stabilized condition.

The primary objective of the study was to establish that therapy with fondaparinux was noninferior to enoxaparin with respect to death, MI, or refractory ischemia at 9 days. Secondary outcomes included evaluating these same end points at 30 days and again at the end of the study. The main safety outcome was bleeding at 9 days.

The enrolled patients were of relatively high risk, more than half with suspected MI, but most were treated conservatively, because only about 34% of each group underwent percutaneous coronary intervention (PCI) during the initial hospitalization. Otherwise, the patients received aggressive medical therapy, including aspirin in 97% of cases, clopidogrel in about 70%, and statin therapy in 79%. Approximately 9% of patients in both arms of the trial had disease of sufficient severity to warrant coronary artery bypass grafting.⁴

At 9 days of follow-up, fondaparinux met the noninferiority criterion, with 5.8% of patients in both arms experiencing the primary end point. At 30 days, there was a trend favoring patients randomized to fondaparinux with respect to the combination of death, MI, and refractory ischemia. This trend was driven by a small but significant reduction in mortality among patients randomized to fondaparinux (2.9% vs 3.5%; $P = .02$). These differences held up at 180 days as well, when mortality was significantly lower among patients randomized to fondaparinux than those treated with enoxaparin (5.8% vs 6.5%; $P = .05$).

With respect to safety, there was an excess of bleeding complications in the enoxaparin arm at 9 days, 30 days, and at the end of the study (Table 1). The authors noted that, regardless of the treatment strategy, bleeding complications were associated with significantly higher rates of death, reinfarction, and stroke. Among the subgroup of patients who underwent PCI ($n = 6899$), outcomes were similar at 9, 30, or 180 days of

Table 1. Results from OASIS-5: Efficacy and Safety of Fondaparinux Versus Enoxaparin

Time and Outcome	Enoxaparin, %	Fondaparinux, %	Hazard Ratio (95% CI)	P Value
9 Days				
Death, MI, or RI	5.7	5.8	1.01 (0.9-1.13)	.0007*
Major bleeding	4.1	2.2	0.52 (0.44-0.61)	<.001
30 Days				
Death, MI, or RI	8.6	8.0	0.93 (0.84-1.02)	.13
Death or MI	6.8	6.2	0.90 (0.81-1.02)	.07
Death	3.5	2.9	0.83 (0.71-0.97)	.02
MI	4.1	3.9	0.94 (0.82-1.08)	
Major bleeding	5.0	3.1	0.62 (0.54-0.72)	<.001
180 Days				
Death, MI, or RI	13.2	12.3	0.93 (0.86-1.00)	.06
Death or MI	11.4	10.5	0.92 (0.84-1.00)	.05
Death	6.5	5.8	0.89 (0.80-1.00)	.05
MI	6.6	6.3	0.95 (0.85-1.06)	
Major bleeding	5.8	4.3	0.72 (0.64-0.82)	<.001

*The results from OASIS-5 demonstrate noninferiority between fondaparinux and enoxaparin at 9 days. Bleeding complications at 9 days were found to be significantly reduced among patients randomized to fondaparinux. On long-term follow-up, there was a small reduction in mortality among patients treated with fondaparinux.

OASIS-5 indicates Fifth Organization to Assess Strategies in Acute Ischemic Syndromes; CI, confidence interval; MI, myocardial infarction; RI, refractory ischemia.

Source: Adapted with permission from Reference 4.

follow-up, regardless of the anticoagulation strategy employed. Bleeding, however, was significantly lower among patients randomized to fondaparinux (Table 2). A clinically significant increase in guiding-wire thrombus formation was noted in the fondaparinux arm (29 vs 8 episodes), but other complications of PCI, such as groin hematomas, were lower among these patients.⁴

OASIS-6: Fondaparinux Versus Enoxaparin in STEMI

Also published this year were the results from the Sixth Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial,⁵ in which patients presenting with STEMI within 24 hours of symptom presentation were randomized to receive antithrombotic therapy with fondaparinux or to “usual care.” This trial was quite complex, because “usual care” could mean UFH or no antithrombotic therapy (placebo).

Additionally, patients were, at the discretion of the enrolling provider, treated with a variety of reperfusion therapies, including PCI or thrombolysis with either a fibrin-specific or nonspecific drug. Given these significant differences, patients in the trial were placed into 1 of 2 large groups. The first (stratum 1) included patients without a strict indication for antithrombotic therapy, typically patients receiving nonfibrin-specific lytics (streptokinase). Stratum 2 included patients in whom antithrombotic therapy was indicated (fibrin-specific lytics, PCI, or no reperfusion therapy).⁵

In stratum 1, a daily subcutaneous dose of 2.5 mg of fondaparinux was compared with a placebo for up to 8 days (or hospital discharge). Patients in stratum 2 were also treated with 2.5 mg/day of fondaparinux or placebo for up to 8 days. Given the firm indication for anticoagulation among these patients, however, patients in the stratum 2–placebo arm were treated with an infusion

Table 2. Results of a Subgroup Analysis of OASIS-5: Safety and Efficacy at 9 Days

A. Primary Efficacy at 9 Days					
Characteristic	No. of Patients	Percentage of Patients With Event		Hazard Ratio	Interaction P Value
		Enoxaparin	Fondaparinux		
Age					
≥65 y	12 261	6.8	6.6		.25
<65 y	7814	4.0	4.4		
Sex					
Men	12 379	6.0	5.8		.48
Women	7699	5.3	5.7		
Creatinine					
At or above median	11 124	6.4	5.9		.07
Less than median	8871	4.9	5.6		
Heparin at randomization					
Yes	3566	6.5	7.1		.43
No	16 512	5.6	5.5		
Revascularization in 9 days					
Yes	7372	9.6	9.9		.47
No	12 706	3.5	3.3		
Catheterization laboratory in center					
Yes	14 028	5.9	6.0		.48
No	6050	5.4	5.1		

B. Major Bleeding at 9 Days					
Characteristic	No. of Patients	Percentage of Patients With Event		Hazard Ratio	Interaction P Value
		Enoxaparin	Fondaparinux		
Age					
≥65 y	12 261	5.5	2.7		.11
<65 y	7814	2.1	1.4		
Sex					
Men	12 379	3.3	2.0		.07
Women	7699	5.5	2.5		
Creatinine					
At or above median	11 124	4.7	2.4		.71
Less than median	8871	3.4	1.9		
Heparin at randomization					
Yes	3566	5.0	3.0		.35
No	16 512	4.0	2.0		
Revascularization at 9 days					
Yes	7372	6.0	4.2		<.001
No	12 706	3.0	1.0		
Catheterization laboratory in center					
Yes	14 028	5.0	2.6		.88
No	6050	2.3	1.2		

OASIS-5 indicates Fifth Organization to Assess Strategies in Acute Ischemic Syndromes.

Source: Reprinted with permission from Reference 4.

Table 3. Results from OASIS-6: Fondaparinux Versus Placebo or UFH

Time and Outcome	Placebo or UFH, %	Fondaparinux, %	Hazard Ratio (95% CI)	P Value
9 Days				
Death or reinfarction	8.9	7.4	0.83 (0.73-0.94)	.003
Death	7.0	6.1	0.87 (0.75-1.00)	.03
Reinfarction	2.3	1.6	0.67 (0.52-0.88)	.004
30 Days*				
Death or reinfarction	11.2	9.7	0.86 (0.77-0.96)	.008
Death	8.9	7.8	0.87 (0.77-0.98)	.03
Reinfarction	3.0	2.5	0.81 (0.65-1.01)	.03
Study End				
Death or reinfarction	14.8	13.4	0.88 (0.79-0.97)	.008
Death	11.6	10.5	0.88 (0.79-0.99)	.03
Reinfarction	4.6	3.8	0.81 (0.65-0.97)	.03
Bleeding Complications at 9 Days				
All severe hemorrhage	1.3	1.0	0.77 (0.55-1.08)	.13
Stratum 1 (vs placebo)	1.6	1.0	0.63 (0.40-1.02)	.06
Stratum 2 (vs UFH)	1.1	1.1	0.95 (0.59-1.52)	.82

*Primary outcome.

The results from OASIS-6 indicate treatment with fondaparinux significantly reduces mortality among patients with STEMI without an increase in severe hemorrhage.

OASIS-6 indicates Sixth Organization for the Assessment Strategies for Ischemic Syndromes; UFH, unfractionated heparin; CI, confidence interval; STEMI, ST-segment elevation myocardial infarction.

Source: Adapted with permission from Reference 5.

of UFH, whereas those in the fondaparinux arm received a matching infusion of a placebo. In both cases, these infusions were continued for 24 to 48 hours. Thus in stratum 2, fondaparinux was compared with UFH, and in stratum 1, the comparator was placebo.⁵

The primary outcome measure was death or recurrent MI at 30 days. Secondary outcomes were death or recurrent infarction at 9 days, 3 months, or 6 months. As with OASIS-5, bleeding complications were the main safety outcome.⁵ A total of 12 092 patients were enrolled in the trial, with 5658 qualifying for stratum 1 and 6434 for stratum 2.

A comparison of baseline characteristics indicated that, for the most part, patients in the 2 strata were similar, with a small excess of patients in stratum 1 presenting with heart failure, and fewer patients receiving aspirin or a thienopyridine or having under-

gone previous revascularization. Reperfusion with thrombolytic therapy (typically streptokinase) was most common in stratum 1 (78%), whereas PCI was more common in stratum 2 (53%). About 23% of patients did not receive reperfusion therapy. The median duration of therapy was 8 days in stratum 1. In stratum 2, UFH was administered for a median of 45 hours and the study drug (or placebo) for a median of 7 days.⁵

With respect to the primary outcome, randomization to fondaparinux resulted in a significant reduction in the rate of death or reinfarction at 30 days (9.7% vs 11.2%; $P = .008$). Significant reductions were also noted at 9 days and at the end of the study (Table 3). Bleeding complications were uncommon in all treatment arms, with the lowest incidence occurring in patients receiving fondaparinux. However, when safety outcomes among patients undergoing PCI were

analyzed in detail, it was noted that there was a trend toward more severe bleeding (16 vs 9), as well as significantly more guiding catheter thrombosis (22 vs 0; $P < .001$), in the fondaparinux arm, compared with the UFH arm. Nevertheless, these events were quite rare, occurring only 16 or 22 times among 1890 patients.⁵

Conclusion

In both OASIS-5 and OASIS-6, therapy with fondaparinux for approximately 8 days was efficacious and safe. Of particular importance were the low rates of severe bleeding in patients treated with fondaparinux in both studies. However, it should be noted that, although the benefit found in these trials may reflect the biochemical superiority of the drug, it might also be due to other factors, such as the longer duration of therapy with fondaparinux or interactions with other evidence-based therapies. Furthermore, according to the results of these studies, therapy with fondaparinux is less likely to be of benefit among ACS patients treated with an early invasive strategy. In all other patient groups studied, however, fondaparinux appears to offer a significant advantage over other anticoagulants, especially with regard to its ability to minimize the risk of bleeding complications. In summary, these large clinical trials clearly suggest the excellent safety and efficacy of fondaparinux, making it a potential therapeutic option in the management of patients presenting with ACS.

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REFERENCES

1. **Thom T, Haase N, Rosemond W, et al.** Heart Disease and Stroke Statistics—2006 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
 2. **Hurst W.** *The Heart, Arteries and Veins*. 10th ed. New York, NY: McGraw-Hill; 2002.
 3. **Moscucci M, Fox KAA, Cannon CP, et al; for the GRACE Investigators.** Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815-1823.
 4. **The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators.** Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354:1464-1476.

5. **The OASIS-6 Trial Group.** Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295:1519-1530.
 6. **Ross R.** Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
 7. **Monroe, DM, Hoffman M, Roberts HR.** Platelets and thrombin generation. *Arterioscler Thromb Vasc Biol*. 2002;22:1381-1389.
 8. **Alban S.** From heparins to factor Xa inhibitors and beyond. *Eur J Clin Invest*. 2005;35(suppl 1):12-20.
 9. **Antman EM, Anbe DT, Armstrong PW, et al.** ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:e82-e292.
 10. **Hirsh J, Raschke R.** Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 suppl):188S-203S.
 11. **Oler A, Whooley MA, Oler J, Grady D.** Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA*. 1996;276:811-815.
 12. **Peterson JE, Mahaffey KW, Hasselblad V, et al.** Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004;292:89-96.
 13. **Warkentin TE, Greinacher A.** Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 suppl):311S-337S.
 14. **Jang IK, Hursting MJ.** When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation*. 2005;111:2671-2683.
 15. **Eikelboom JW, Anand SS, Malmberg K, Weitz JJ, Ginsberg JS, Yusuf S.** Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000;355:1936-1942.
 16. **Cohen M, Demers C, Gurfinkel EP, et al; for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group.** A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med*. 1997;337:447-452.
 17. **The SYNERGY Trial Investigators.** Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45-54.
 18. **Califf RM.** Fondaparinux in ST-segment elevation myocardial infarction: the drug, the strategy, the environment, or all of the above? *JAMA*. 2006;295:1579-1580.
 19. **Wertz J.** Fondaparinux in pulmonary embolism [correspondence]. *N Engl J Med*. 2004;350:619.
 20. **Turpie AGG, Bauer KA, Eriksson BI, Lassen MR; for the Steering Committee of the Pentasaccharide Orthopedic Prophylaxis Studies.** Fondaparinux vs enoxaparin for the prevention of venous thromboem-

bolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med.* 2002;162:1833-1840.

21. Spruill WJ, Wade WE, Leslie RB. A cost analysis of fondaparinux versus enoxaparin in total knee arthroplasty. *Am J Ther.* 2004;11:3-8.

22. Sullivan SD, Davidson BL, Kahn SR, Muntz JE,

Oster G, Raskob G. A cost-effectiveness analysis of fondaparinux sodium compared with enoxaparin sodium as prophylaxis against venous thromboembolism: use in patients undergoing major orthopaedic surgery. *Pharmacoeconomics.* 2004;22:605-620.

23. Gallus AS, Coghlan D. Heparin pentasaccharide. *Curr Opin Hematol.* 2002;9:422-429.