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Update

Antithrombotics and Thrombolytics for the Treatment of Acute Coronary Syndromes

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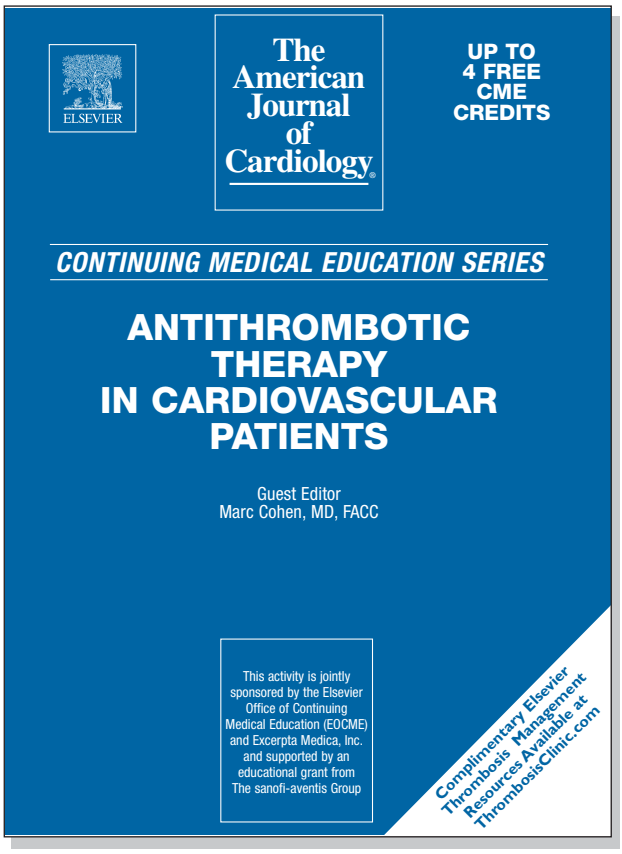

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Antithrombotics and Thrombolytics for the Treatment of Acute Coronary Syndromes

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INTRODUCTION

There has been remarkable progress in the development of new drugs for the treatment of coronary thrombotic disorders during the past 3 decades. Advances in biotechnology and improved methods of synthesis have yielded several new drugs that have been added to the standard agents for antithrombotic treatment (**Table 1**). Newer agents include the antithrombotics (low-molecular-weight heparins [LMWHs], direct thrombin inhibitors, and factor Xa inhibitors); the antiplatelet drugs (adenosine diphosphate [ADP] antagonists and the glycoprotein [GP] IIb/IIIa receptor inhibitors); and the recombinant fibrinolytic agents. Use of these drugs in combination has become the standard of care in acute coronary syndromes (ACS). The term *ACS* is used to cover a group of clinical symptoms compatible with acute myocardial ischemia that result from coronary artery diseases. These include unstable angina (UA) and the closely related non–ST-segment elevation myocardial infarction (NSTEMI), which are associated with an increased risk of death and myocardial infarction (MI); and ST-segment elevation myocardial infarction (STEMI), which requires immediate reperfusion therapy (thrombolysis) or percutaneous coronary intervention (PCI).[1–3] In fact, the American College of Cardiology/American Heart Association (ACC/AHA) 2002 guidelines recommend a combination of aspirin, a heparin, and a GP IIb/IIIa inhibitor as the most effective therapy in patients with UA/NSTEMI, including those who are scheduled to undergo PCI.[1] Moreover, the 2004 American College of Chest Physicians (ACCP) guidelines recommend the use of a fibrinolytic agent with adjunctive anticoagulant and antiplatelet agents depending on the clinical presentation.[2]

Table 1. Antithrombotic and Fibrinolytic Agents Used for Acute Coronary Syndromes

Anticoagulants	Antiplatelet agents	Fibrinolytic agents
• Unfractionated heparin	• Aspirin	• Streptokinase
• Low-molecular-weight heparins (eg, enoxaparin, dalteparin)	• Adenosine diphosphate receptor blockers (eg, ticlopidine, clopidogrel)	• Recombinant tissue plasminogen activator (eg, alteplase, reteplase, tenecteplase)
• Direct thrombin inhibitors (eg, argatroban, bivalirudin, hirudin)	• Glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban)	

The effects of drugs given in combination cannot be predicted reliably even when extensive data are available on the individual clinical effects of each drug. Information on the mechanism of action, pharmacokinetics, and pharmacodynamics of medications may suggest combinations that could be beneficial, but clinical trials are necessary to determine if the combination therapy is efficacious in a particular patient population. The dosage and timing of administration of these agents may have an effect on the outcome as well. In the case of anticoagulants, antiplatelet agents, and thrombolytics in patients with ACS, combination treatment may also increase the rate of adverse events, particularly bleeding. In recent years, a number of combinations of anticoagulants, antiplatelet agents, and thrombolytics have been tested in clinical trials in patients with ACS, leading to changes in clinical practice and improvements in patient morbidity and mortality. This article will provide a review of the clinical trial data on various combinations of these agents, focusing on the interactions between antithrombotics and drugs that are frequently used in combination with them in the treatment of patients with ACS.

OVERVIEW OF PHARMACOLOGY

UFH

Unfractionated heparin (UFH) is a heterogeneous mixture of glycoaminoglycans of varying molecular size, with a molecular weight ranging from 3000 to 30,000 daltons (mean 15,000 daltons).[4] UFH is an indirect anticoagulant that requires a plasma cofactor, antithrombin (AT). The heparin/AT complex inactivates thrombin factor IIa, and factors IXa, Xa, XIa, and XIIa. The binding of UFH to AT occurs primarily through a unique glucosamine unit contained within a pentasaccharide sequence.[5] Additionally, UFH binds to a number of plasma proteins, blood cells, and endothelial cells that modify its physiologic effect.[4] In an ex vivo study, Aggarwal et al found that, in the presence of tirofiban, anticoagulation with therapeutic doses of UFH significantly increased platelet reactivity compared with either enoxaparin or bivalirudin.[6] UFH may also induce immune-mediated platelet activation, leading to heparin-induced thrombocytopenia (HIT) in addition to adverse effects on bone metabolism that may result in osteoporosis.[4,7]

Continuous IV infusion and SC injection are the 2 preferred routes of administration of UFH.[4] However, plasma recovery of UFH is reduced when it is administered SC in low (eg, 5000 U q12h) or moderate (eg, 12,500 or 15,000 U q12h) doses. At doses >35,000 U over 24 hours, however, plasma recovery is almost complete.

LMWHs

Different and distinct LMWHs are formed by depolymerization of UFH, depending on which patented procedure is used. LMWHs are relatively more potent in the catalyzation of the inhibition of factor Xa by AT than in the inactivation of thrombin. Although there are individual differences, the mean molecular weight of currently available LMWHs ranges from 4000 to 5000 daltons.[4] LMWHs do not only exhibit physical and chemical heterogeneity but variability in biologic actions, which are translated into differences in clinical effects as well.

The pharmacokinetic properties of LMWHs are superior to those of UFH. For example, bioavailability of SC bolus injections approaches 100% at low doses and peak anti-factor X activity occurs 3 to 5 hours after SC injection, with a more predictable dose-response compared with UFH. LMWHs are also associated with a longer, non–dose-dependent half-life than UFH. Effective SC dosing of LMWHs provides potential major clinical benefits including the potential for an earlier, more rapid treatment, the ability to treat prehospitalization, and decreased medication errors, all of which are important for improved clinical outcomes.[2] Other theoretical advantages of the LMWHs over UFH include less protein and endothelial cell binding, and a more predictable degree of anticoagulation without the need for close laboratory monitoring. LMWHs are also less likely to activate platelets, and are less likely to cause thrombocytopenia or osteopenia than UFH. These features along with the body of evidence from clinical trials favor their use in ACS.[1,8,9]

Nevertheless, LMWHs have been associated with increased rates of minor bleeding, which is generally characterized as cutaneous (at the injection site) and oral.[1] Additionally, there has been some reservation about the use of LMWHs in patients undergoing invasive surgical procedures because of the longer half-life and the fact that the anticoagulation effect is not easily reversed. However, clinical data are emerging that support the use of LMWHs, especially enoxaparin, in more invasive procedures.[8,9]

Factor Xa Inhibitors (Pentasaccharides)

Clinical trials have shown the efficacy of pentasaccharides for the prevention and treatment of venous thromboembolism and for the treatment of arterial thrombosis.[10] Fondaparinux is a synthetic analog of the pentasaccharide sequence found in heparin and LMWHs that is responsible for binding to AT.[10] The fondaparinux/AT complex is a strong inhibitor of factor Xa. Fondaparinux shares many of the advantages of the LMWHs: it is administered SC, requires no monitoring, and is less likely to cause thrombocytopenia or osteopenia. It has excellent plasma availability and a long half-life. It also shares the disadvantage of not being easily reversed. It is approved for treatment of acute deep vein thrombosis and pulmonary embolism, as well as for venous thromboembolism prophylaxis in at-risk patients undergoing abdominal surgery or any of several types of orthopedic surgery.

Direct Thrombin Inhibitors

These agents specifically and directly block thrombin without the need for a cofactor such as AT. Hirudin, a 65-amino-acid polypeptide, binds directly to thrombin receptors producing potent and predictable anticoagulation.[1] Hirudin is indicated for anticoagulation in patients with HIT and for the prophylaxis of deep vein thrombosis in patients undergoing hip-replacement surgery.[1] Hirudin may have some potential advantages over UFH. It has the ability to inhibit clot-bound thrombin, it is not inhibited by activated platelets, it does not require a cofactor, and it may provide a more stable anticoagulant response.[2]

Bivalirudin is a small 20 amino-acid peptide modeled after the hirudin molecule. It binds specifically and reversibly to active thrombin in a bivalent fashion.[1] Bivalirudin acts initially as a noncompetitive thrombin inhibitor and subsequently as a competitive univalent inhibitor, allowing complex, transient inhibition of thrombin. Unlike heparin, bivalirudin inhibits free and unbound thrombin, thus inhibiting both initiation and continuation of clot formation. It does not induce platelet activation or aggregation, which is an additional advantage over heparin.[11] However, the ACCP 2004 guidelines reserve use of the direct thrombin inhibitors to patients with known or suspected HIT; the ACCP recommends the combination of hirudin with tissue plasminogen activator (t-PA) (Grade 1A) or bivalirudin with streptokinase (Grade 2A).[2]

Aspirin/Nonsteroidal Anti-inflammatory Drugs

Aspirin has been and remains the foundation of antithrombotic treatment regimens in patients with ACS. Aspirin irreversibly inhibits cyclo-oxygenase-1 within platelets, preventing the formation of thromboxane A2 and diminishing platelet formation.[1] A synergistic effect is observed when aspirin is combined with other agents. In the Second International Study of Infarct Survival (ISIS-2), streptokinase and aspirin both reduced mortality when compared with placebo (25% vs 23%, respectively), while the combination of aspirin with streptokinase reduced mortality by 42% (8% vs 13.2%; $P < 0.001$) when compared with placebo.[2]

The use of aspirin with UFH has raised some concerns. Although aspirin irreversibly binds cyclo-oxygenase-1, a transient reversal of this effect occurs in response to arachidonic acid during carotid endarterectomy or PCI in a small number of patients. This may be the result of the impact of UFH on endothelial cells causing platelet activation. The clinical significance of this observation is currently unknown.[12]

Additionally, in a post hoc analysis of 2 clinical trials, ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) and PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms), Lancaster et al[13] observed that patients presenting with UA/NSTEMI who have received prior aspirin therapy often fail therapy with UFH. Use of enoxaparin or the combination of tirofiban with UFH was more effective than UFH alone in these patients. It was postulated that prior use of aspirin may render thrombi less thrombin-dependent and more platelet-dependent. Recent findings with hirudin showed that agents with a strong AT effect tend to prevent thrombin-mediated platelet activation. The fact that LMWHs have less effect on platelet aggregation than UFH may explain the observations in these studies.[13]

ADP Antagonists

The ADP antagonists, ticlopidine and clopidogrel, are antiplatelet agents with a mode of action that differs from that of aspirin. These thienopyridine derivatives inhibit platelet aggregation induced by ADP. Combining these drugs with aspirin may have an additive effect. As with other antithrombotic agents used in combination, the use of clopidogrel and aspirin is associated with increased bleeding.[14]

Because of the delayed onset of action (several days for a complete antiplatelet effect), these drugs are not considered to be first-line agents in the acute setting and are indicated only for use in patients who are unable to tolerate aspirin. Clopidogrel is the preferred ADP antagonist because of its slightly faster onset of action and potentially better adverse event profile.[1]

GP IIb/IIIa Inhibitors

The platelet GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) block fibrinogen from binding to the platelet GP IIb/IIIa receptors.[1] Abciximab has

been shown to reduce tissue-factor thrombin generation, prothrombin, microparticle release, and mural thrombus formation.[3] In vitro studies with GP IIb/IIIa inhibitors have shown dose-dependent decreases in prothrombinase activity and thrombin activity. When GP IIb/IIIa inhibitors are combined with heparins, thrombin generation is further reduced: the greatest reductions are seen in combination with enoxaparin.[3]

The GP IIb/IIIa inhibitors and the AT agents target different but complementary physiological mechanisms. GP IIb/IIIa inhibitors prevent platelet aggregation and the formation of platelet-rich thrombi, which are the primary causes of ischemic complications in non–ST-elevation ACS and PCI, while the AT agents inhibit the thrombin-mediated deposition of fibrin that stabilizes the platelet-rich thrombus. In a crossover study in healthy subjects, UFH and LMWH showed similar effects on the pharmacokinetics and pharmacodynamics of eptifibatide. The investigator concluded that LMWH can be substituted for UFH in combination with eptifibatide in NSTEMI.[15]

Fibrinolytic Agents

The fibrinolytic agents include streptokinase and the recombinant t-PAs. The differentiating characteristics of these agents are outlined in **Table 2.**[2]

The benefits of streptokinase infusion have been known for more than 40 years and set the stage for the current use of fibrinolytic agents in STEMI. Over the past decade, attention has been focused on improving the potency, efficacy, and ease of administration of fibrinolytic agents.[2] Streptokinase continues to be widely used, but the t-PAs have proven to be both effective and safe. Tenecteplase, a genetically engineered variant of alteplase, has become the new standard for fibrinolytic therapy. It can be administered in a bolus and has been associated with less bleeding. In the treatment of STEMI, standard treatment is a fibrinolytic agent combined with UFH, although major bleeding has been problematic. The primary predictors of bleeding with this combination are prolongation of activated partial thromboplastin time (aPTT) and fibrinogen degradation. In vitro studies have shown that alteplase or reteplase combined with UFH significantly prolonged aPTT compared with UFH alone, whereas tenecteplase is associated with attenuation of aPTT prolongation. Tenecteplase may interfere with the anticoagulation properties of UFH because of its fibrin specificity and may have a lesser effect on fibrinogen breakdown than do the other t-PAs.[16] In in vitro studies, tenecteplase combined with UFH resulted in shortened aPTT compared with UFH alone. Further evaluation of this interaction as well as the interaction of tenecteplase and LMWH is necessary.[16]

CLINICAL TRIALS WITH COMBINATION THERAPY

UA/NSTEMI

UA is defined as angina pectoris or equivalent ischemic discomfort with at least one of the following characteristics of chest or arm discomfort: may occur at rest or with minimal exertion and lasting >10 minutes, severe and of new onset (within the prior 4–6 weeks), and/or crescendo pattern (more severe, prolonged, or frequent than previously). The diagnosis of NSTEMI is established if a patient with clinical

Table 2. Characteristics of Fibrinolytic Agents[2]

Agent	Source	Fibrin Specific	Mode of Action	Half-life (minutes)	Dosing
Streptokinase	Group A streptococci		Activator complex	18–23	1-hour infusion
Alteplase	Recombinant, human t-PA	++	Direct	3–8	Bolus, 90-minute infusion
Reteplase	Recombinant, human mutant t-PA	+	Direct	15–18	Double bolus
Tenecteplase	Recombinant plus mutation	+++	Direct	18–20	Single bolus

t-PA = tissue plasminogen activator.
Adapted with permission from Menon et al. *Chest.* 2004;126:549–575.

features of UA develops signs of myocardial necrosis, evidenced by elevated cardiac biomarkers and with no or transient elevation of ST segment on the electrocardiogram (ECG).

Treatment goals in UA/NSTEMI include modifying the disease process and slowing the progression to more serious adverse cardiac events. A large body of literature and clinical experience support the use of various combinations of AT and antiplatelet agents. The 2002 ACC/AHA guidelines recommend use of both UFH and LMWH depending on the clinical presentation.[1] The guidelines recommend that all patients with possible ACS be given aspirin. If ACS is likely or definite, patients should receive IV heparin or SC LMWH in addition to aspirin. When definite ACS is accompanied by continuing ischemia or there are high-risk features, a GP IIb/IIIa inhibitor should be given in addition to aspirin and heparin. A GP IIb/IIIa inhibitor is also recommended if an intervention is planned such as PCI or coronary artery bypass graft (CABG).

Combination Therapy With LMWHs or UFH

Clinical studies in the 1980s demonstrated the benefits of aspirin and UFH, alone and in combination, compared with placebo in patients with ACS. For example, in the acute phase of UA, both aspirin and UFH reduced the incidence of MI, with a trend favoring UFH. However, aspirin plus heparin was not superior to heparin alone and was associated with slightly more complications.[17] Additional trials investigated the potential advantages of combination therapy with aspirin and UFH over aspirin monotherapy. Consistent trends across each study favored combined pharmacotherapy for its ability to reduce death or MI. Evidence has also emerged supporting the use of UFH in combination with either aspirin alone or in combination with a GP IIb/IIIa inhibitor in higher-risk patients or those undergoing early PCI.[1]

Over the past decade, growing literature has supported the use of LMWHs as a substitute for UFH in patients with UA/NSTEMI, including high-risk patients. Despite the advances in the acute management of patients with UA/NSTEMI, the risk of future life-threatening ischemic events remains. The addition of the GP IIb/IIIa inhibitors to UFH-containing regimens has resulted in significant benefits for those patients considered to be intermediate or high risk. Multiple studies have assessed the use of LMWHs as an alternative to UFH in combination with GP IIb/IIIa inhibitors.

The GUSTO-IV (Global Utilization of Streptokinase and Tissue-plasminogen Activator for Occluded Arteries) ACS study[18] enrolled 7800 patients. The majority received treatment with UFH and abciximab. In a subset of patients (n = 974) in which dalteparin was substituted for UFH, transfusions, major and minor bleeding rates, and types of bleeding were not significantly different from those of the population as a whole. Combination with abciximab in both heparin groups was associated with increased major and minor bleeding. The increased number of minor bleeding incidents with LMWH was attributable to hematomas at injection sites. In combination with abciximab, lower doses of dalteparin are recommended, especially in older patients and in women. In patients who had invasive procedures, between-group bleeding rates were similar. Increased thrombocytopenia was observed with the addition of abciximab in both treatment groups. There was no difference in efficacy between the dalteparin and UFH groups.[18]

The ACUTE (Antithrombotic Combination Using Tirofiban and Enoxaparin) II trial[19] evaluated tirofiban in combination with enoxaparin or UFH, in a blinded, randomized study. Of the 525 patients evaluated, 210 patients received UFH and 315 received enoxaparin. In general, there were very few significant bleeding events. TIMI (Thrombolysis In Myocardial Infarction) major bleeding rates were 0.3% for enoxaparin versus 1.0% for UFH; minor bleeding rates were 2.5% for enoxaparin versus 4.3% for UFH. Minor bleeding was mostly oral and at injection sites. The cutaneous bleeding rate was higher in the enoxaparin group. Death/MI rates were similar in the 2 groups. However, patients who received enoxaparin had more favorable outcomes with respect to refractory ischemia requiring revascularization and rehospitalization for UA.[19]

The INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment) trial[20] strongly favored an enoxaparin/eptifibatide combination compared with UFH/eptifibatide. High-risk patients (N = 746) were evaluated in this randomized, open-label study. The

enoxaparin group had significantly lower rates of major bleeding at 96 hours (1.8% vs 4.6%; $P = 0.03$), with no intracranial hemorrhage, but the rate of minor bleeding was higher with enoxaparin (30.3% vs 20.8%; $P = 0.003$). The enoxaparin group had a lower rate of death or MI at 30 days compared with UFH and eptifibatide (5% vs 9%; $P = 0.031$). Lower rates of ischemia were observed in the enoxaparin group (14.3% vs 25.4%, $P = 0.0002$ for 48 hours, and 12.7% vs 25.9%, $P < 0.0001$ for 48–96 hours).[20]

The A to Z study showed that the use of enoxaparin with tirofiban is a suitable alternative to UFH and tirofiban in high-risk patients.[8] In this prospective, randomized, open-label study of 3987 patients that compared tirofiban in combination with either enoxaparin or UFH, primary and secondary end points favored the enoxaparin group, except death, which occurred in only 1% of all patients. Rates were low for any TIMI grade bleeding (enoxaparin 3% and UFH 2.2%). The incidence of major bleeding was 0.9% with enoxaparin and 0.4% with UFH. There were no between-group differences in major bleeds in patients who underwent early interventions. The design of this study met prespecified criteria for noninferiority, with a 1% absolute benefit and a 12% relative benefit favoring the enoxaparin combination.[8]

ACUITY (Acute Catheterization and Urgent Intervention and Triage Strategy Trial)[21] compared 3 pharmacologic treatments for patients with UA or NSTEMI. All patients received aspirin and were randomized to receive: UFH or enoxaparin plus a GP IIb/IIIa inhibitor (n = 4603), bivalirudin with a GP IIb/IIIa inhibitor (n = 4604), or bivalirudin alone (n = 4612). Within 72 hours, 56.7% of the patients underwent PCI, 11.1% underwent surgical revascularization, and 32.5% received medical therapy. Bivalirudin treatment alone was found to be superior to combination treatment with UFH or enoxaparin plus a GP IIb/IIIa inhibitor in major bleeding (3.0% vs 5.7%; $P < 0.001$) and in the composite net clinical benefit defined as a combination of the ischemic composite and major bleeding (10.1% vs 11.7%; $P = 0.015$).[21]

The ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2) trial[22] evaluated 2022 high-risk ACS patients undergoing PCI who received a high (600-mg) loading dose of clopidogrel 2 hours prior to the procedure, along with 500-mg oral or IV aspirin. Patients were randomized to receive abciximab or placebo plus heparin to determine if treatment with the GP IIb/IIIa inhibitor abciximab would reduce the composite end point of death, MI, or urgent target vessel revascularization at 30 days. The results showed that in patients who received pretreatment with clopidogrel, the primary composite end point of death, MI, or urgent target vessel revascularization due to myocardial ischemia within 30 days was reduced in the abciximab group in comparison with the placebo group (8.9% vs 11.9%; relative risk [RR] = 0.75; $P = 0.03$).[22]

Most trials evaluating the use of LMWHs have excluded patients with renal dysfunction, which is a risk factor for vascular disease and a predictor of bleeding. Analyses of data from the Global Registry of Acute Coronary Events (GRACE) (N = 11,881) showed that LMWH is as effective as or superior to UFH in preventing ischemic events in patients with NSTEMI, even in those with renal dysfunction.[23] Combination therapy with LMWH and a GP IIb/IIIa inhibitor seems to be better tolerated than UFH plus a GP IIb/IIIa inhibitor, regardless of renal status. LMWH alone was associated with a lower risk of mortality compared with UFH alone (4.2% vs 6.2%, $P < 0.0001$). LMWH alone resulted in fewer major bleeding incidents than UFH (2.1% vs 3.3%, $P = 0.0006$). This benefit was found irrespective of renal status, but remained nonsignificant in patients with severe renal dysfunction. There was a similar reduction in major bleeding with LMWH combined with a GP IIb/IIIa inhibitor compared with UFH and a GP IIb/IIIa inhibitor (4.3% vs 6.9%, $P = 0.0420$). A similar but nonsignificant trend was observed in patients with renal dysfunction.[23]

Refer to **Appendix 1** for a summary of trials in patients with NSTEMI receiving combination therapy.

STEMI

The diagnosis of STEMI is established if a patient develops clinical symptoms of myocardial necrosis and is evidenced by elevated serum cardiac biomarkers and elevated ST-segment on the ECG.

In patients with STEMI, the goal is to achieve both short- and long-term arterial reperfusion to attenuate

the progression of adverse cardiac events. Standard thrombolytic therapy includes aspirin, a fibrinolytic agent, heparin, and, increasingly, a GP IIb/IIIa inhibitor. UFH continues to be the standard antithrombin, despite its potential therapeutic disadvantages. UFH interferes with thrombin activity but it does not inhibit the production of thrombin, which may lead to subsequent thrombotic events. Agents that act earlier in the coagulation cascade may be associated with a lower risk for thrombosis.[24] LMWH potentially offers a more stable and predictable anticoagulant effect, simple bolus administration, and greater inhibition of thrombin generation. Other advantages of LMWH include a greater capacity to release tissue factor pathway inhibitor, a lower propensity to promote activation and aggregation of platelets, and potential antiplatelet effects via a higher degree of suppression of von Willebrand factor.[24]

Fibrinolytic Agents With UFH or LMWH

Although UFH has been the standard of care, the evidence for combining UFH with fibrinolytic agents is strong for t-PA (alteplase), but less strong with streptokinase. Despite the benefits seen with IV UFH, the increase in major bleeding and intracranial hemorrhage led to reduced doses of UFH in the GUSTO IIb and TIMI 9B studies.[2]

The HART II (Second Trial of Heparin and Aspirin Reperfusion Therapy), AMI-SK, and ASSENT-3 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen) trials showed that coronary patency rates are improved with enoxaparin and that enoxaparin may also be related to improved tissue-level profusion. In regimens that include the specific fibrinolytic agents (t-PAs) studies have shown UFH and aspirin to improve coronary patency. In patients receiving the fibrinolytic agent streptokinase, UFH is not recommended.[24–26]

In the HART II study,[24] all patients (N = 400) received aspirin and recombinant alteplase and were randomly assigned to receive either enoxaparin or UFH. Enoxaparin was at least as effective as UFH in restoring patency. Enoxaparin also trended towards higher rates of recanalization and lower rates of reocclusion. Adverse events were similar in both groups.[24]

The AMI-SK study[25] assessed 496 patients with STEMI treated with aspirin and streptokinase and randomized to receive either placebo or enoxaparin as adjunctive therapy. The enoxaparin group did better than the placebo group with early reperfusion and reduced risk of reocclusion. By day 30 there were more hemorrhages in the enoxaparin group, but the difference was not statistically significant.[25]

In the large, open-label, randomized ASSENT-3 trial[26] (N = 6095), patients received full-dose tenecteplase plus enoxaparin; half-dose tenecteplase and weight-adjusted low-dose UFH, plus an infusion of abciximab; or full-dose tenecteplase and weight-adjusted low-dose UFH. Adjunctive therapy with either enoxaparin or abciximab resulted in greater improvement in coronary complications than with heparin. Based on the efficacy and safety results, tenecteplase plus enoxaparin was the most effective combination.[26]

In the ENTIRE-TIMI 23 open-label study,[27] patients were randomized to receive standard reperfusion therapy (full-dose tenecteplase) or combination therapy (half-dose tenecteplase plus abciximab), and either UFH or enoxaparin. Results indicate similar early reperfusion with both enoxaparin and UFH, with enoxaparin showing benefit over UFH with respect to ischemic events through 30 days, with similar risk for major bleeding. When the combination of half-dose tenecteplase plus abciximab was compared with full-dose tenecteplase at 60 minutes, similar reperfusion rates were observed and at 180 minutes there was a trend towards more complete ST-segment resolution, regardless of AT agent.[27]

In the NRMI (National Registry of Myocardial Infarction) STEMI registry,[28] 2482 patients receiving a GP IIb/IIIa inhibitor and LMWH were compared with 34,838 patients treated with UFH. Major bleeding occurred in 4% of LMWH-treated patients versus 4.2% of those treated with UFH, with a trend towards fewer recurrences of acute MI in the LMWH group.[28]

The results of the ASSENT-PLUS trial[29] underscored the need for continuous assessment of LMWH. In this open-label, randomized study performed in the prehospitalization setting, there was an increase in the rate of major hemorrhage and intracranial hemorrhage with enoxaparin versus UFH in patients treated with t-PA for STEMI before hospital arrival. However, almost all cases of hemorrhage

occurred in patients >75 years old.[29] As a result of this study, the dose of enoxaparin was then adjusted in the pivotal ExTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)-TIMI 25 trial to 0.75 mg/kg SC BID in patients 75 years or older.[30]

ExTRACT-TIMI 25[30,31] was a randomized, controlled, double-blind trial comparing UFH with enoxaparin as adjunctive therapy in fibrinolytic treatment of STEMI. Patients with planned fibrinolytic treatment were randomized to receive UFH for 48 hours (n = 10,223) or enoxaparin 30 mg IV bolus plus 1 mg/kg SC BID for the duration of the index hospitalization (n = 10,256). Patients aged 75 years or older received no IV bolus and the SC dose was reduced to 0.75 mg/kg BID. The IV loading dose was omitted and a 25% reduction in the maintenance dose of enoxaparin was selected for patients who developed or were discovered to have renal impairment (creatinine clearance ≤30 mL/min). There was a significant 33% reduction in the RR of MI and a 26% reduction in the need for urgent revascularization at 30 days in the enoxaparin group. Death or MI at 30 days occurred in 9.9% of the patients in the enoxaparin group, compared with 12.0% of the patients in the UFH group (RR reduction = 17%, $P < 0.001$). The rate of intracranial hemorrhage was the same in both treatment groups, but major bleeding at 30 days was increased in the enoxaparin group compared with UFH (1.4% vs 2.1%; RR = 53%; $P < 0.001$). The results demonstrated that in patients receiving fibrinolysis for STEMI for 48 hours, treatment with enoxaparin through the index hospitalization was superior when compared with UFH.[31]

OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) is another recent trial that analyzed the STEMI patient population.[32] This trial evaluated fondaparinux versus standard approaches to antithrombotic therapy in patients with STEMI in preventing the primary and composite end points of death or reinfarction at 30 days. OASIS-6 was a randomized, double-blind, controlled trial in patients with STEMI comparing fondaparinux to a control group consisting of patients receiving UFH or placebo. The 12,092 patients with STEMI were randomized to receive fondaparinux 2.5 mg once daily for up to 8 days (n = 6036) or control (n = 6056), which consisted of UFH bolus injection of 60 IU/kg followed by an infusion of 12 IU/kg/h for 24 to 48 hours followed by placebo for up to 8 days or placebo in patients for whom heparin was not indicated. The primary end point was decreased in the fondaparinux group compared with the control group (9.7% vs 11.2%; hazard ratio [HR] = 0.86; $P = 0.008$). The reduction in the primary end point at 30 days in the fondaparinux group was driven by comparison with the placebo group. There was no difference in the primary efficacy end point when patients who received fondaparinux were compared with those who received UFH (8.3% vs 8.7%; HR = 0.96; P = NS). Fondaparinux was superior to placebo in reducing death or MI at 30 days in patients with STEMI.[32] Essentially, the results of OASIS-6 should be interpreted cautiously and are in favor of fondaparinux versus placebo but not fondaparinux versus UFH. It does not appear that the dose of fondaparinux tested in OASIS-6 is adequate for primary PCI in patients with STEMI.

The current ACCP recommendation for patients aged <75 years with preserved renal function (creatinine levels <2.5 mg/dL in male patients and <2.0 mg/dL in female patients) is enoxaparin (30-mg bolus IV followed by 1 mg/kg SC q12h) with tenecteplase up to 7 days (Grade 2B).[2]

Refer to **Appendix 2** for a summary of trials in patients with STEMI receiving combination therapy.

PCI

Despite innovations in techniques, use of stents, and newer, more effective, and safer antiplatelet agents, optimal antithrombotic treatment regimens for PCI need to be further elucidated. Published literature supports the use of low-dose UFH with a GP IIb/IIIa inhibitor in ACS patients during PCI. There is also a growing body of evidence validating LMWHs as adjunctive therapy for PCI.[33]

Khosla et al[34] found encouraging safety and efficacy results in a prospective study of enoxaparin and eptifibatide in 56 patients undergoing PCI. Major bleeding occurred in 1 of 56 patients (2%); there were no vascular complications in this small study.[34]

An earlier pilot study[35] showed similar favorable results with dalteparin and abciximab. The combination of dalteparin with abciximab was studied in

107 patients randomized to receive 40 or 60 IU/kg of dalteparin IV. The higher dose of dalteparin provided greater efficacy and a more consistent antithrombotic effect with no apparent increase in bleeding rates.[35]

An observational study[33] with a lower dose of enoxaparin (0.5 mg/kg) in 242 patients (26% received concomitant abciximab) found very low rates of bleeding and ischemic complications with enoxaparin. The prespecified anticoagulant effect (target anti-Xa >0.5 IU) was achieved in most patients. Similar anticoagulation and safety were observed irrespective of advanced age, renal dysfunction, body weight, or the use of eptifibatide. No enoxaparin dose adjustments were needed in combination with eptifibatide.[33]

Another small (N = 75) observational study[36] found encouraging results with the 0.5 mg/kg IV dose of enoxaparin combined with abciximab, eptifibatide, or tirofiban in a population of 67 outpatients with positive stress test results and 8 inpatients with recent ACS. No major bleeding or adverse cardiac events occurred through 30 days posthospitalization, and the minor TIMI bleeding rate was <2%. These benefits were seen even in patients with high-risk lesions and multivessel interventions, the majority with stents (87%).[36]

Two parallel-group, prospective studies, NICE (National Investigators Collaborating on Enoxaparin) 1 and 4,[37] evaluated the use of LMWH in patients undergoing elective PCI. NICE 1 evaluated enoxaparin (1 mg/kg) alone in 828 patients and NICE 4 evaluated a reduced dose of enoxaparin (0.75 mg/kg) with the standard dose of abciximab in 818 patients. NICE 4 was the first large-scale trial that evaluated enoxaparin and abciximab during PCI. Enoxaparin, used alone or in combination, provided safe and effective anticoagulation during PCI. In both studies bleeding events were infrequent.[37]

Comparative, randomized studies with standard therapies further confirm the efficacy of LMWH as an alternative to UFH during PCI. Galeote et al[38] compared abciximab with enoxaparin or UFH as adjuvant therapy during percutaneous transluminal coronary angioplasty in a prospective, randomized, nonblinded study (N = 99). They concluded that adjuvant treatment with enoxaparin and abciximab during PCI was safe and associated with a low incidence of adverse events. There was a trend towards less major bleeding and less of an increase in creatinine kinase with enoxaparin compared with UFH.[38]

Another randomized study[39] (N = 162) compared enoxaparin, enoxaparin plus abciximab, and UFH as adjunctive therapy during PCI. All patients received aspirin and ticlopidine for 3 days prior to PCI. No major cardiac events occurred in any of the treatment groups. There was a similar low rate of major or minor bleeding events. Both enoxaparin groups had less of an increase in necrosis markers post-PCI and a reduced number of ischemic events compared with UFH.[39]

The NICE 3 observational study[9] was initiated to assess the safety and efficacy of enoxaparin combined with GP IIb/IIIa inhibitors in higher-risk patients, including those who go on to PCI.[9] Of the 707 patients enrolled, 671 were treated with enoxaparin, and 628 of these patients also received a GP IIb/IIIa inhibitor. Of the 286 patients who underwent PCI, 283 also received a GP IIb/IIIa inhibitor. The combination of enoxaparin and a GP IIb/IIIa inhibitor was associated with a low incidence of bleeding. The overall 30-day incidence of non-CABG-related bleeding was 1.9%, which is consistent with an estimated historical rate of 2%. Major and non-CABG-related bleeding occurred in a small percentage of patients who underwent PCI. Death occurred at hospital discharge in 1.0% of patients, and 1.6% at 30 days; MI occurred in 3.5% and 5.1% of patients, respectively; and urgent revascularization occurred in 2.7% and 6.8%, respectively. The investigators concluded that the combination of enoxaparin and a GP IIb/IIIa inhibitor was safe, even in patients undergoing subsequent PCI.[9]

The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial[40] compared enoxaparin with UFH in patients at high risk for ischemic events. This was a prospective, randomized, open-label, multicenter study in 10,027 patients intended for PCI. A majority of patients (92%) enrolled in this study underwent PCI. Use of GP IIb/IIIa inhibitors was not mandated. Results from this study did not show either superiority or inferiority with enoxaparin compared with UFH. The primary

end point, death or nonfatal MI by 30 days, occurred in 14.0% and 14.5% of patients, with enoxaparin and UFH, respectively. Bleeding was moderately increased in the enoxaparin group, with no significant differences with respect to transfusions or intracranial hemorrhage.[40]

The ASPIRE (Arixtra Study in Percutaneous Coronary Intervention: A Randomized Evaluation) trial[41] was a pilot study in a total of 350 patients, comparing fondaparinux and UFH with and without GP IIb/IIIa inhibitors. Patients undergoing PCI were randomized to receive UFH (n = 117), 2.5 mg fondaparinux IV (n = 118), or 5 mg fondaparinux IV (n = 115). The randomization was stratified depending on whether GP IIb/IIIa inhibitors were planned. Efficacy and safety were similar in the fondaparinux and UFH groups. There were no significant differences in outcomes between those who received GP IIb/IIIa inhibitors and those who did not. This suggests that fondaparinux may be substituted for UFH in PCI.[41]

The STEEPLE (Safety and Efficacy of GP IIb/IIIa Inhibitors With Intravenous Enoxaparin in Patients Undergoing Elective Percutaneous Coronary Intervention) trial[42] evaluated 3528 patients undergoing a nonemergent PCI. Patients were randomized to 0.5 or 0.75 mg/kg enoxaparin IV or UFH regimen adjusted by activated clotting time. Patients given enoxaparin experienced a 57% reduction in major bleeding compared with UFH ($P < 0.01$). The composite ischemic end points were similar. There was an increase in bleeding when GP IIb/IIIa inhibitors were used (10.3% vs 5.0% without GP IIb/IIIa inhibitors; $P < 0.001$), as well as ischemic events (8.1% vs 5.2%, $P < 0.001$). Multivariate analysis showed that the use of GP IIb/IIIa inhibitors was independently correlated with bleeding (odds ratio [OR] = 2.3 [1.7–3.0]; $P < 0.0001$), but not with ischemic events, regardless of the anticoagulant used. The study indicates that enoxaparin may be a suitable alternative to UFH for patients undergoing elective PCI. The use of GP IIb/IIIa inhibitors with enoxaparin or UFH was associated with an increase in bleeding.[42] More clinical studies should be performed to draw any solid conclusions.

Refer to **Appendix 3** for a summary of trials in patients undergoing PCI and receiving combination therapy.

SUMMARY

In selecting treatment for patients with ACS, clinicians must depend on the results of clinical trials. There is no other way to predict with certitude whether a combination of drugs will be beneficial or whether the risk of adverse events will outweigh the benefits of treatment. Fortunately, more combinations of agents are being tested in well-designed trials, providing a base of evidence to support decisions in clinical practice.

Aspirin is the mainstay of antithrombotic regimens in patients with ACS. UFH is still commonly used in UA/NSTEMI and STEMI. However, because of its mechanism and pharmacodynamic/pharmacokinetic profile, it is not always the ideal agent—monitoring and dose adjustments are required, its use is not recommended with streptokinase, and there is an increased risk for bleeding. Evidence from clinical trials clearly supports the substitution of UFH with LMWH, because of the physiologic effects of LMWH and its pharmacokinetic and pharmacodynamic profile.

Successful outcomes in clinical studies have eased concerns about potential adverse bleeding events and difficulties in reversing the antithrombotic effects of LMWH. Most of the clinical trial data is based on enoxaparin and, as a result, the ACCP 2004 recommendations for LMWH with fibrinolytics are specific for enoxaparin. Because of successes in treating patients in the acute setting, current studies are focused on early use of antithrombotic agents in the prehospitalization setting to further improve outcomes.

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Appendix 1. Summary of Clinical Trials in Patients With NSTEMI Receiving Combination Therapy

Trial	Methods	Results/Conclusions
GUSTO-IV[1] **Objective:** Investigate the safety and efficacy of abciximab + UFH vs LMWH (dalteparin) in ACS **Drugs:** Abciximab, UFH, dalteparin; all patients received aspirin **Patient Population:** 7800	Patients were randomized to receive abciximab for 24 hours or 48 hours, or placebo in a double-blind, double-dummy fashion. In the dalteparin substudy patients received 5 days of SC dalteparin instead of a 48-hour infusion of UFH. All patients received aspirin.	Addition of abciximab to UFH or LMWH and aspirin as primary treatment of ACS is not associated with any significant reduction in cardiac events but a doubled risk of bleeding compared with placebo. In the dalteparin cohort, major and minor bleeding occurred in 5.0% of patients in the abciximab groups compared with 1.8% of patients in the placebo group ($P < 0.05$). In the UFH cohort the difference between the abciximab and placebo groups was similar (3.8% vs 1.8%, $P < 0.001$). At 30 days there were no significant differences in the rate of death or MI, either in the dalteparin (abciximab 9.6% vs placebo 11.3%: OR: 0.85; 95% CI: 0.58–1.25) or in the UFH cohort (8.5% vs 7.6%; OR: 1.12; CI: 0.95–1.34). The combination of abciximab with dalteparin seems as safe as abciximab plus UFH, although nuisance bleedings are more common.
ACUTE II[2] **Objective:** Estimate the incidence of bleeding complications and collect data on clinical efficacy of tirofiban + enoxaparin + aspirin **Drugs:** Tirofiban, enoxaparin, UFH; all patients received aspirin. **Patient Population:** 525	Patients were randomized to receive tirofiban with either SC enoxaparin (1 mg/kg q12h) or aPTT-adjusted IV UFH (1.5–2.5 times control) in a 2:3 double-blind, double-dummy fashion. Therapy was administered for 24–96 hours. Bleeding incidences were assessed until 24 hours after trial therapy was discontinued; other clinical outcomes were assessed for as long as 30 days.	Incidence of total TIMI bleeding events was 4.8% in the tirofiban/UFH group vs 3.5% in the tirofiban/enoxaparin group (OR: 1.4; 95% CI: 0.6–3.4). The incidence of any bleeding event was 34.3% vs 54.6%, respectively. Most bleeds were cutaneous. Although not powered to compare ischemic end points, refractory ischemia requiring urgent intervention (4.3% vs 0.6%, $P = 0.01$) and rehospitalization for unstable angina (7.1% vs 1.6%, $P = 0.002$) were observed more frequently in the tirofiban/UFH group compared with the tirofiban/enoxaparin group.
INTERACT[3] **Objective:** Determine the rates of major hemorrhage and ischemia in GP IIb/IIIa inhibitor-treated patients receiving enoxaparin vs UFH **Drugs:** Eptifibatide, enoxaparin, UFH; all patients received aspirin **Patient Population:** 746	All patients received eptifibatide and aspirin and were randomized to receive, in an open-label manner, either SC enoxaparin (1 mg/kg q12h) for 48 hours or aPTT-adjusted UFH infusion (1.5–2 times control) for 48 hours.	Major non-coronary artery bypass surgery-related bleeding at 96 hours (primary safety outcome) was significantly lower among enoxaparin-treated patients than among heparin-treated patients (1.8% vs 4.6%, $P = 0.03$). Minor bleeding was more frequent in the enoxaparin group (30.3% vs 20.8%, $P = 0.003$). Less ischemia as detected by continuous ECG evaluation (primary efficacy outcome) was seen in the enoxaparin group during the initial (14.3% vs 25.4%, $P = 0.002$) and subsequent (12.7% vs 25.9%, $P < 0.0001$) 48-hour monitoring periods. The rate of death or MI at 30 days was significantly lower in the enoxaparin group (5% vs 9%, $P = 0.031$).
A to Z Trial[4] **Objective:** Phase A: Assess efficacy and safety of enoxaparin compared with UFH in patients with non–ST-segment elevation ACS receiving concomitant tirofiban and aspirin **Drugs:** Tirofiban, enoxaparin, UFH; all patients received aspirin **Patient Population:** 3987	Phase A of the A to Z study was a multicenter, prospective, open-label, randomized noninferiority trial to compare SC enoxaparin (1 mg/kg q12h) with weight-adjusted UFH infusion in patients receiving tirofiban and aspirin.	A total of 169 (8.4%) of 2018 patients randomized to receive enoxaparin experienced death, MI, or refractory ischemia at 7 days compared with 184 (9.4%) of 1952 patients randomized to receive UFH (HR: 0.88; 95% CI: 0.71–1.08). This met the prespecified criterion for noninferiority. Rates for any TIMI grade bleeding were low (3.0% for enoxaparin and 2.2% for UFH; $P = 0.13$).

continued

Appendix 1. Continued

Trial	Methods	Results/Conclusions
ACUITY[5] **Objective:** Determine if bivalirudin compared with UFH or LMWH in combination with GP IIb/IIIa inhibitors was more effective **Drugs:** UFH, enoxaparin, GP IIb/IIIa inhibitor, bivalirudin; all patients received aspirin **Patient Population:** 13,819	Prospective, randomized comparison of 3 treatments for patients with unstable angina or NSTEMI.	For the intent-to-treat population, the combination of bivalirudin and GP IIb/IIIa inhibitor was noninferior to UFH/enoxaparin and GP IIb/IIIa inhibitor for all primary end points. Bivalirudin alone was superior to the combination of UFH/enoxaparin and GP IIb/IIIa inhibitor in major bleeding (3.0% vs 5.7%; $P < 0.001$ for superiority). The primary net clinical benefit was significantly improved in the bivalirudin-alone group compared with the UFH/enoxaparin plus GP IIb/IIIa group (10.1% vs 11.7%; $P = 0.015$ for superiority).
ISAR-REACT 2[6] **Objective:** Determine if abciximab is associated with clinical benefit in high-risk patients with ACS undergoing PCI after pretreatment with clopidogrel **Drugs:** Heparin, abciximab, placebo; all patients received clopidogrel and aspirin **Patient Population:** 2022	Patients were randomly assigned to receive abciximab plus UFH or placebo plus UFH in a double-blind, placebo-controlled manner. The primary end point was a composite of death, MI, or urgent target vessel revascularization occurring within 30 days after randomization.	The primary end point was reached in 90 patients (8.9%) assigned to abciximab vs 120 (11.9%) assigned to placebo for a 25% reduction in risk with abciximab (RR: 0.75; 95% CI: 0.58–0.97; $P = 0.03$). Among patients with an elevated troponin level, the incidence of ischemic events was significantly lower in the abciximab group (67/513 patients [13.1%]) compared with the placebo group (98/536 patients [18.3%]) (RR: 0.71; 95% CI: 0.54–0.95; $P = 0.02$) ($P = 0.7$ for interaction).

NSTEMI = non–ST-elevation myocardial infarction; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; ACS = acute coronary syndrome; MI = myocardial infarction; OR = odds ratio; CI = confidence interval; aPTT = activated partial thromboplastin time; GP = glycoprotein; ECG = electrocardiogram; HR = hazard ratio; PCI = percutaneous coronary intervention; RR = relative risk.

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Appendix 2. Summary of Clinical Trials in Patients With STEMI Receiving Combination Therapy With Fibrinolytic Agents

Trial	Methods	Results/Conclusions
HART II[1] **Objective:** Demonstrate noninferiority of enoxaparin vs UFH in efficacy measured by the 90-minute TIMI 2 and 3 reperfusion with alteplase **Drugs:** Enoxaparin, UFH, alteplase; all patients received aspirin **Patient Population:** 400	After enrollment, all patients received aspirin and underwent thrombolysis with alteplase with the accelerated infusion regimen. Patients allocated to enoxaparin received 30-mg IV bolus followed by 1 mg/kg SC q12h. Patients in the UFH group received an initial IV bolus (4000 U for those weighing up to 67 kg; 5000 U for patients weighing >67 kg), followed by an infusion of 15 U/kg per hour for at least 3 days, adjusted to achieve a target aPTT of 2–2.5 times control. Coronary angiography was performed 90 minutes after the initial bolus alteplase dose and repeated for reocclusion assessment after 5–7 days.	Patency rates (TIMI grades 2 and 3) of the infarct-related artery 90 minutes after start of therapy were 80.1% in patients treated with enoxaparin compared with 75.1% in the UFH group. The noninferiority of enoxaparin when compared with UFH was confirmed per protocol. A total of 259 patients with TIMI 2 or 3 flow on the initial angiogram and with an assessable angiogram at follow-up were assessed for reocclusion. Reocclusion, defined as deterioration from TIMI grade 2 or 3 at 90 minutes to grade 0 or 1 at follow-up, occurred in 5.9% and 9.8% of patients in the enoxaparin and UFH groups, respectively. Reocclusion of TIMI grade 3 arteries occurred in 3.1% and 9.1% of enoxaparin- and UFH-treated patients ($P = 0.12$).
AMI-SK[2] **Objective:** Determine if addition of enoxaparin to streptokinase improves early and sustained coronary patency and clinical outcome in patients with evolving MI **Drugs:** Enoxaparin, streptokinase, aspirin, placebo **Patient Population:** 496	All patients were treated with IV streptokinase and aspirin. In a double-blind fashion, patients were randomized to receive either enoxaparin (n = 253) IV bolus (30 mg) and then SC injections (1 mg/kg q12h) or placebo (n = 243) for 3–8 days. The median duration of treatment in both groups was 5 days.	ST-segment resolution at 90 minutes and 180 minutes measured by ECG was improved in patients receiving enoxaparin. Complete, partial, and no ST-segment resolution at 180 minutes was observed in 36.3%, 44.4%, and 19.2% in the enoxaparin group vs 25.4%, 43.5%, and 31.6% in the placebo group, respectively ($P = 0.014$). Assessment of the primary end point revealed improved TIMI-3 flow with enoxaparin vs placebo (70.3% vs 57.8%, $P = 0.01$). Combined TIMI-2 and -3 flow was also improved (87.6% vs 71.7%, $P = 0.001$), as was TIMI frame count ($P = 0.003$). The triple clinical end point of death, reinfarction, and recurrent angina at 30 days was reduced with enoxaparin (13.4% vs 21.0%, $P = 0.03$). By day 30, more major hemorrhages occurred in the enoxaparin group vs the placebo group (4.8% vs 2.5%, $P = 0.2$).
ASSENT-3[3] **Objective:** Compare efficacy and safety of tenecteplase plus enoxaparin or abciximab, with that of tenecteplase plus weight-adjusted UFH in patients with acute MI **Drugs:** Tenecteplase, enoxaparin, UFH, abciximab **Patient Population:** 6095	Patients were randomly assigned to 1 of 3 regimens: full-dose tenecteplase and enoxaparin for a maximum of 7 days (enoxaparin group; n = 2040), half-dose tenecteplase with weight-adjusted low-dose UFH and a 12-hour infusion of abciximab (abciximab group; n = 2017), or full-dose tenecteplase with weight-adjusted UFH for 48 hours (UFH group; n = 2038). The primary end points were the composites of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia (efficacy end point), and the above end point plus in-hospital intracranial hemorrhage or in-hospital major bleeding complications (efficacy plus safety end point). Analysis was by intention to treat.	There were significantly fewer efficacy end points in the enoxaparin and abciximab groups than in the UFH group: 233/2037 (11.4%) vs 315/2038 (15.4%; RR: 0.74 [95% CI: 0.63–0.87], $P = 0.0002$) for enoxaparin, and 223/2017 (11.1%) vs 315/2038 (15.4%; RR: 0.72 [95% CI: 0.61–0.84], $P < 0.0001$) for abciximab. The same was true for the efficacy plus safety end point: 280/2037 (13.7%) vs 347/2036 (17.0%; RR: 0.81 [95% CI: 0.70–0.93], $P = 0.0037$) for enoxaparin, and 287/2016 (14.2%) vs 347/2036 (17.0%; RR: 0.84 [95% CI: 0.72–0.96], $P = 0.01416$) for abciximab. The tenecteplase plus enoxaparin or abciximab regimens reduced the frequency of ischemic complications of an acute MI. Tenecteplase plus enoxaparin seems to be an attractive alternative reperfusion regimen that warrants further study.

continued

Appendix 2. Continued

Trial	Methods	Results/Conclusions
ENTIRE-TIMI 23[4] **Objective:** Evaluate enoxaparin and full-dose tenecteplase and half-dose tenecteplase plus abciximab **Drugs:** Tenecteplase, abciximab, UFH, enoxaparin; all patients received aspirin **Patient Population:** 483	In this open-label study, patients were randomized to receive either standard reperfusion (full-dose tenecteplase) or combination therapy (half-dose tenecteplase plus abciximab) and to either a control group using UFH or enoxaparin. To provide a concurrent control group while obtaining more information regarding the experimental enoxaparin regimens, randomization ratios of either 1:2 or 1:3 were used (UFH: enoxaparin).	With full-dose tenecteplase and UFH the rate of TIMI 3 flow at 60 minutes was 52% and was 48%–51% with enoxaparin. Using combination therapy the rate of TIMI 3 flow at 60 minutes was 48% with UFH and 47%–58% with enoxaparin. The rate of TIMI 3 flow among all UFH patients was 50% and was 51% among all enoxaparin patients. Through 30 days, death/MI occurred in the full-dose tenecteplase group in 15.9% of patients with UFH and 4.4% with enoxaparin ($P = 0.005$). In the combination therapy group, the rates were 6.5% with UFH and 5.5% with enoxaparin. The rate of major hemorrhage with full-dose tenecteplase was 2.4% with UFH and 1.9% with enoxaparin; with combination therapy it was 5.2% with UFH and 8.5% with enoxaparin.
ASSENT-3 PLUS[5] **Objective:** Study the feasibility and treatment delays and compare efficacy and safety of the 2 antithrombin cotherapies with tenecteplase in the prehospital setting **Drugs:** Tenecteplase, enoxaparin, UFH **Patient Population:** 1639	In the prehospital setting, patients with STEMI were randomly assigned to receive tenecteplase and either enoxaparin IV bolus of 30 mg followed by 1 mg/kg SC BID for a maximum of 7 days or weight-adjusted UFH for 48 hours. The median delay from symptom onset to tenecteplase administration was 115 minutes.	The primary efficacy end point (the composite of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia) tended to be lower with enoxaparin compared with UFH (14.2% vs 17.4%, $P = 0.080$), and there was a smaller, nonsignificant trend for the primary efficacy and safety end point (18.3% vs 20.3%, $P = 0.297$). There were reductions in in-hospital reinfarction (3.5% vs 5.8%, $P = 0.028$) and refractory ischemia (4.4% vs 6.5%, $P = 0.067$) but increases in total stroke (2.9% vs 1.3%, $P = 0.026$) and intracranial hemorrhage (2.20% vs 0.97%, $P = 0.047$). The increase in stroke and intracranial hemorrhage was seen in patients >75 years of age. The combination of tenecteplase with enoxaparin reduced early ischemic events, but lower doses of enoxaparin need to be tested in elderly patients.
ExTRACT-TIMI 25[6,7] **Objective:** Test if enoxaparin, when compared with UFH, reduces the composite end point of all-cause mortality and nonfatal MI within 30 days after randomization in patients with STEMI who receive fibrinolytic therapy **Drugs:** Fibrinolytic therapy with streptokinase, alteplase, tenecteplase, or reteplase, enoxaparin, UFH; all patients received aspirin **Patient Population:** 20,506	Using a double-blind, double-dummy design, patients with STEMI who were scheduled to undergo fibrinolysis were randomized to receive either enoxaparin throughout the index hospitalization or weight-based UFH for at least 48 hours. For patients <75 years of age, enoxaparin (or matching placebo) was to be given as a fixed 30-mg IV bolus followed 15 minutes later by an SC injection of 1.0 mg/kg q12h. For patients ≥75 years of age, the IV bolus was eliminated and the SC dose was reduced to 0.75 mg/kg q12h. In patients with a creatinine clearance of <30 mL/min, the dose was modified to 1.0 mg/kg q24h. The primary efficacy end point was death or nonfatal recurrent MI through 30 days.	The primary end point occurred in 12.0% of patients in the UFH group and 9.9% of those in the enoxaparin group (17% reduction in relative risk, $P < 0.001$). Nonfatal reinfarction occurred in 4.5% of the patients receiving UFH and 3.0% of those receiving enoxaparin (33% reduction in RR, $P < 0.001$); 7.5% of patients given UFH died, as did 6.9% of those given enoxaparin ($P = 0.11$). The composite of death, nonfatal reinfarction, or urgent revascularization occurred in 14.5% of patients given UFH and 11.7% of those given enoxaparin ($P < 0.001$); major bleeding occurred in 1.4% and 2.1%, respectively ($P < 0.001$). The composite of death, nonfatal reinfarction, or nonfatal intracranial hemorrhage (a measure of net clinical benefit) occurred in 12.2% of patients given UFH and 10.1% of those given enoxaparin ($P < 0.001$).

continued

Appendix 2. Continued

Trial	Methods	Results/Conclusions
OASIS-6[8] **Objective:** Evaluate the effect of fondaparinux when initiated early and given for up to 8 days vs usual care (placebo in those in whom UFH is not indicated [stratum 1] or UFH for up to 48 hours followed by placebo for up to 8 days [stratum 2]) in patients with STEMI **Drugs:** Fondaparinux, UFH, placebo **Patient Population:** 12,092	Randomized, double-blind comparison of fondaparinux 2.5 mg once daily or control for up to 8 days in patients with STEMI. From day 3 through day 9, all patients received either fondaparinux or placebo according to the original randomized assignment. Composite of death or reinfarction at 30 days (primary) with secondary assessments at 9 days and at final follow-up (3 or 6 months).	Death or reinfarction at 30 days was significantly reduced from 677 (11.2%) of 6056 patients in the control group to 585 (9.7%) of 6036 patients in the fondaparinux group (HR: 0.86; 95% CI: 0.77–0.96; $P = 0.008$; absolute risk reduction: 1.5%; 95% CI: 0.4%–2.6%). These benefits were observed at 9 days (537 [8.9%] placebo vs 444 [7.4%] fondaparinux; HR: 0.83; 95% CI: 0.73–0.94; $P = 0.003$), and at study end (857 [14.8%] placebo vs 756 [13.4%] fondaparinux; HR: 0.88; 95% CI: 0.79–0.97; $P = 0.008$). Mortality was significantly reduced throughout the study. There was no heterogeneity of the effects of fondaparinux in the 2 strata by planned UFH use. There was no benefit in patients undergoing primary PCI. In patients in stratum 2, fondaparinux was superior to UFH in preventing death or reinfarction at 30 days (HR: 0.82; 95% CI: 0.66–1.02; $P = 0.08$) and at study end (HR: 0.77; 95% CI: 0.64–0.93; $P = 0.008$). Significant benefits were observed in those receiving thrombolytic therapy (HR: 0.79; $P = 0.003$) and those not receiving any reperfusion therapy (HR: 0.80; $P = 0.03$). There was a tendency to fewer severe bleeds (79 for placebo vs 61 for fondaparinux; $P = 0.13$), with significantly fewer cardiac tamponade (48 vs 28; $P = 0.02$) with fondaparinux at 9 days. In patients with STEMI, particularly those not undergoing primary PCI, fondaparinux significantly reduced mortality and reinfarction without increasing bleeding and strokes.

STEMI = ST-elevation myocardial infarction; UFH = unfractionated heparin; aPTT = activated partial thromboplastin time; MI = myocardial infarction; ECG = electrocardiogram; RR = relative risk; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention.

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Appendix 3. Summary of Clinical Trials in Patients Undergoing PCI and Receiving Combination Therapy

Trial	Methods	Results/Conclusions
Khosla et al[1] **Objective:** Evaluate the safety and efficacy of coadministration of IV enoxaparin and eptifibatide during nonemergent coronary and peripheral vascular intervention **Drugs:** Enoxaparin, eptifibatide, aspirin, clopidogrel **Patient Population:** 56	All patients were pretreated with 325 mg aspirin daily for at least 3 days before the procedure. At the beginning of the procedure, 0.75 mg/kg enoxaparin and a 180-µg/kg bolus of eptifibatide were administered IV. An IV infusion of eptifibatide at a dose of 2 µg/kg per minute was initiated. At 10 minutes after bolus administration of eptifibatide, a platelet aggregation study was done to assess platelet inhibition and achieve platelet inhibition of ≥94%. If the platelet inhibition was <90%, a second bolus of 180 µg/kg of eptifibatide was administered. Eptifibatide was continued for a mean of 17 ± 6 hours postprocedure. All patients received 75 mg clopidogrel orally for 4 weeks postprocedure.	The procedural success rate was 99% (92/93 procedures), the acute clinical success rate was 98% (54/55 patients), the major complication rate was 2% (1/56 patients), and the vascular complication rate was 2% (1/56 patients). The use of IV enoxaparin in conjunction with IV eptifibatide during nonemergent coronary and peripheral vascular intervention is safe and effective and eliminates the need for routine measurement of ACT during the procedure.
Kereiakes et al[2] **Objective:** Assess anticoagulant effect and clinical safety for multiple dose regimens of dalteparin administered either SC before PCI or IV at the time of PCI in combination with abciximab initiated at the time of the procedure **Drugs:** Abciximab, dalteparin, clopidogrel; all patients received aspirin **Patient Population:** 107	Patients without prior SC dalteparin therapy or >12 hours after an SC dose were randomly allocated in a blinded fashion to receive either 40 (n = 27) or 60 (n = 28) IU/kg dalteparin IV at the time of PCI. After observing thrombus during PCI, the blind was broken and all subsequent patients received 60 IU/kg (no randomization). All patients received oral aspirin before PCI and daily thereafter. Oral clopidogrel was initiated after coronary stent deployment.	Patients who received 60 IU/kg of dalteparin IV had a lower incidence of procedural thrombosis (0% vs 11.1%, $P < 0.01$), more consistent antithrombotic effect (anti-factor Xa activity), and a similar incidence of major bleeding (3.7% vs 2.6%) compared with patients who received 40 IU/kg of IV dalteparin. Dalteparin appears to be safe and effective when administered in conjunction with abciximab for PCI.
Choussat et al[3] **Objective:** Examine low-dose IV enoxaparin in elective PCI and its applicability to an unselected population regardless of age, weight, renal function, or use of GP IIb/IIIa inhibitors **Drugs:** Enoxaparin, eptifibatide **Patient Population:** 242	Consecutive patients undergoing PCI were treated with a single IV bolus of enoxaparin (0.5 mg/kg), and 26% of patients (n = 64) also received eptifibatide. Sheaths were removed immediately after the procedure in patients treated with enoxaparin only, and 4 hours after the procedure in those also treated with eptifibatide.	A peak anti-Xa >0.5 IU/mL was obtained in 97.5% of the population, and 94.6% of patients had their peak anti-Xa level in the predefined target range of 0.5 to 1.5 IU/mL. Advanced age, renal failure, being overweight, and eptifibatide use did not alter the anticoagulation profile. At 1-month follow-up, 6 patients (2.5%) had died, had an MI, or had undergone an urgent revascularization; all the patients had an anti-Xa level >0.5 IU/mL during PCI. Patients without an ischemic event and without a CK increase, but with a detectable troponin release in the next 24 hours of PCI (>2 µg/mL, n = 21), had similar anti-Xa levels as those without troponin elevation. There were 1 major and 3 minor bleeding events that were not associated with anti-Xa overshoot. Low-dose enoxaparin appears to be safe and effective and does not require dose adjustment when used with eptifibatide.
Carnendran et al[4] **Objective:** Observe the safety and efficacy of a lower dose of IV enoxaparin (0.5 mg/kg) in conjunction with any GP IIb/IIIa inhibitor **Drugs:** Enoxaparin, GP IIb/IIIa inhibitor, aspirin, clopidogrel **Patient Population:** 75	Eligible PCI patients received 0.5 mg/kg IV enoxaparin and a GP IIb/IIIa inhibitor. None received anticoagulation 24 hours prior to PCI; all received preprocedural aspirin, postprocedural deployment of the Angio-Seal, and clopidogrel therapy.	TIMI minor bleeding was 1.3%; there were no TIMI major bleeding events or major adverse cardiac events during in-hospital stay or at 30-day follow-up. IV enoxaparin appeared safe and effective during PCI when given at a low dose in conjunction with GP IIb/IIIa inhibitor and Angio-Seal.

continued

Appendix 3. Continued

Trial	Methods	Results/Conclusions
NICE 1 and NICE 4[5] **Objective:** Evaluate the safety and utility of specific dose regimens for enoxaparin both with and without concomitant abciximab during PCI **Drugs:** Enoxaparin, abciximab, ticlopidine, clopidogrel; all patients received aspirin **Patient Population:** 828 in NICE 1 and 818 in NICE 4	Patients in NICE 1 received enoxaparin 1.0 mg/kg IV at PCI. Patients in NICE 4 received enoxaparin 0.75 mg/kg IV in combination with standard-dose abciximab IV immediately preceding PCI. Patients with coronary stent deployment also received either oral ticlopidine or clopidogrel for 30 days.	Bleeding events and ischemic outcomes were assessed in-hospital and 30 days after PCI and were infrequent with either pharmacologic regimen. Enoxaparin with or without abciximab provided safe and effective anticoagulation during PCI.
Galeote et al[6] **Objective:** Evaluate the safety of combined enoxaparin and abciximab compared with standard therapy using UFH and abciximab **Drugs:** Abciximab, enoxaparin, UFH, ticlopidine **Patient Population:** 99	Before beginning the procedure, all patients received a loading dose of IV aspirin (500 mg). The patients randomly received an IV bolus of enoxaparin (0.75 mg/kg) or UFH (70 U/kg). All patients received an IV bolus of abciximab (0.25 mg/kg) followed by a 12-hour IV infusion. All patients received 500 mg of oral ticlopidine at the end of the procedure.	There was less major bleeding in the enoxaparin group (2%) than in the UFH group (8.2%) but the difference was not statistically significant. There were no significant differences in the frequency of in-hospital clinical events. There was a lower increase in aPTT at 5 hours in the enoxaparin vs UFH group (P = 0.02). It was impossible to remove the introducer in 7 of the UFH group patients due to aPTT >60 seconds as opposed to 1 patient in the enoxaparin group. Postprocedural CK elevation occurred in 8.0% of the enoxaparin group and in 6.1% of the UFH group (P = NS). No thrombocytopenia was observed in either group. Enoxaparin/abciximab was safe and associated with a low incidence of major bleeding and major ischemic in-hospital events.
Dudek et al[7] **Objective:** Assess the efficacy and safety of combined abciximab and enoxaparin vs enoxaparin administration during PTCA of complex (B2 or C) lesions **Drugs:** Enoxaparin, abciximab, UFH; all patients were pretreated for 3 days with aspirin and ticlopidine **Patient Population:** 162	Patients were randomized to 1 of 3 groups: UFH (n = 50) adjusted to ACT >300 seconds, enoxaparin (n = 58; IV 1 mg/kg), and ReoEnox (n = 54) receiving enoxaparin (IV 0.75 mg/kg) followed by abciximab (IV bolus 0.25 mg/kg and 0.125 µg/kg/min 12-hour infusion). Serial CK, CK-myocardial bound (0, 8, 16, 24, 48 h) and cardiac troponin T and troponin I (0, 24, 48 h) were obtained after PTCA.	There were no major cardiac events (death, large MI, re-PTCA, CABG) in any group, but the biochemical markers were distinct. Despite standard therapies (aspirin + UFH + ticlopidine), there was a relatively high occurrence of peri-PTCA myocardial damage. The use of enoxaparin reduced the number of ischemic events and the combination of enoxaparin and abciximab appears safe. There was no additional benefit of abciximab against myocardial damage in patients with ticlopidine pretreatment and application of enoxaparin during PTCA.
NICE-3[8] **Objective:** Examine the safety and efficacy of combined use of enoxaparin and 1 of the 3 commercially available GP IIb/IIIa inhibitors in patients with ACS, and determine the feasibility and safety of bringing patients who had already received SC enoxaparin to the catheterization laboratory for coronary intervention, if necessary, without the supplemental use of UFH **Drugs:** Enoxaparin, abciximab, tirofiban, eptifibatide, clopidogrel; all patients received aspirin **Patient Population:** 671	Of 671 patients, 628 (93.6%) received combined therapy with enoxaparin and a GP IIb/IIIa inhibitor, while 43 patients (6.4%) received enoxaparin alone. There was no specific protocol regarding the exact timing of PCI after enrollment. Of the 286 patients undergoing PCI, 100 (35%) received supplemental IV enoxaparin, and 224 (78%) received at least 1 dose of clopidogrel before PCI. There were 59 patients (21%) who received a GP IIb/IIIa inhibitor only at the time of PCI, with infusions continued after the procedure.	The primary end point of non-CABG major bleeding in patients who received enoxaparin and GP IIb/IIIa treatment was reached by 12 of 628 patients, or 1.9% (95% CI: 0.8%–3.0%). The cumulative 30-day incidence of major bleeding was 8.3%. Patients who underwent PCI accounted for a minority of the total number of patients who developed major bleeding (6/52) and non-CABG major bleeding (4/12). Patients undergoing PCI can be safely managed with enoxaparin and a GP IIb/IIIa inhibitor.

continued

Appendix 3. Continued

Trial	Methods	Results/Conclusions
SYNERGY[9] **Objective:** Compare the outcomes of patients treated with enoxaparin vs UFH and define the role of enoxaparin in patients with non–ST-segment elevation ACS at high risk for ischemic cardiac complications managed with an early invasive approach **Drugs:** Enoxaparin, UFH **Patient Population:** 10,027	Patients were randomized to receive either weight-adjusted IV UFH to aPTT of 1.5–2.0 times normal or SC enoxaparin 1 mg/kg q12h. The primary efficacy outcome was the composite clinical end point of all-cause death or nonfatal MI during the first 30 days after randomization. The primary safety end point was major bleeding or stroke.	The primary end point occurred in 14.0% (696/4993) of patients assigned to enoxaparin and 14.5% (722/4985) of patients assigned to UFH (OR: 0.96; 95% CI: 0.86–1.06). No differences in the ischemic events during PCI were observed between enoxaparin and UFH groups, respectively, including similar rates of abrupt closure (31/2321 [1.3%] vs 40/2364 [1.7%]), threatened abrupt closure (25/2321 [1.1%] vs 24/2363 [1.0%]), unsuccessful PCI (81/2281 [3.6%] vs 79/2328 [3.4%]), or emergency CABG surgery (6/2323 [0.3%] vs 8/2363 [0.3%]). More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% vs 7.6%, $P = 0.008$) but nonsignificant excess in GUSTO severe bleeding (2.7% vs 2.2%, $P = 0.08$) and transfusions (17.0% vs 16.0%, $P = 0.16$). Enoxaparin is a safe and effective alternative to UFH.
ASPIRE[10] **Objective:** Determine safety and feasibility of fondaparinux in the PCI setting **Drugs:** UFH, fondaparinux, GP IIb/IIIa inhibitor **Patient Population:** 350	Patients undergoing PCI were randomized in a blinded manner to receive UFH, 2.5 mg fondaparinux IV, or 5.0 mg fondaparinux IV. Randomization was stratified for planned or no planned use of GP IIb/IIIa inhibitors. The primary safety outcome was total bleeding, which was a combination of major and minor bleeding events.	The incidence of total bleeding was 7.7% in the UFH group and 6.4% in the combined fondaparinux groups (HR: 0.81; 95% CI: 0.35–1.84; $P = 0.61$). Bleeding was less common in the 2.5-mg fondaparinux group compared with the 5-mg fondaparinux group (3.4% vs 9.6%, $P = 0.06$). The composite efficacy outcome of all-cause mortality, MI, urgent revascularization, or need for a bailout GP IIb/IIIa inhibitor was 6.0% in the UFH group and 6.0% in the fondaparinux group, with no significant difference in efficacy among the fondaparinux doses compared with UFH. Coagulation marker analysis at 6 and 12 hours after PCI demonstrated that fondaparinux was superior to UFH in inducing a sustained reduction in markers of thrombin generation, as measured by prothrombin fragment F1.2 ($P = 0.02$). Fondaparinux was comparable to UFH for clinical safety and efficacy outcomes.
STEEPLE[11] **Objective:** Compare the efficacy and safety of a GP IIb/IIIa inhibitor used as an adjunct to UFH or enoxaparin **Drugs:** Enoxaparin, UFH, GP IIb/IIIa inhibitor **Patient Population:** 3528	Randomization was stratified by the physician's choice of GP IIb/IIIa inhibitor use. The primary efficacy end point was the composite of death, nonfatal MI, and urgent target vessel revascularization. Non–CABG-related bleeding was the primary safety end point.	Patients given enoxaparin experienced a 57% reduction in major bleeding compared with UFH ($P < 0.01$). The composite ischemic end points were similar. When GP IIb/IIIa inhibitors were used, bleeding increased (10.3% with vs 5.0% without GP IIb/IIIa inhibitors, $P < 0.001$), as did ischemic events (8.1% vs 5.2%, $P < 0.001$). Multivariate analysis showed that use of GP IIb/IIIa inhibitors was independently correlated with bleeding (OR: 2.3 [1.7–3.0]; $P < 0.001$), but not with ischemic events, regardless of the anticoagulant choice. Enoxaparin can be a suitable alternative to UFH for patients undergoing elective PCI.

PCI = percutaneous coronary intervention; ACT = activated clotting time; GP = glycoprotein; MI = myocardial infarction; CK = creatine kinase; UFH = unfractionated heparin; aPTT = activated partial thromboplastin time; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; ACS = acute coronary syndrome; CI = confidence interval; OR = odds ratio; HR = hazard ratio.

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