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Official publication of the American College of Chest Physicians



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Chest 2008;133;670S-707S
DOI 10.1378/chest.08-0691

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ISSN:0012-3692



Antithrombotic Therapy for Non-ST-Segment Elevation Acute Coronary Syndromes*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about antithrombotic therapy for coronary artery disease is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggestions are weaker as there is uncertainty regarding the benefits, risks and costs such that individual patients' values may lead to different choices (for a full understanding of the grading see the "Grades of Recommendation for Antithrombotic Agents" chapter by Guyatt et al, *CHEST* 2008; 133[suppl]:123S–131S). Among the key recommendations are the following: for all patients presenting with non-ST-segment elevation (NSTEMI) acute coronary syndrome (ACS), without a clear allergy to aspirin, we recommend immediate aspirin (162 to 325 mg po) and then daily oral aspirin (75 to 100 mg) [Grade 1A]. For NSTEMI ACS patients who are at at least moderate risk for an ischemic event and who will undergo an early invasive management strategy, we recommend "upstream" treatment either with clopidogrel (300 mg po bolus, followed by 75 mg/d) or a small-molecule IV glycoprotein (GP) IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A]. For NSTEMI ACS patients who are at least moderate risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, we recommend "upstream" treatment with clopidogrel (300 mg oral bolus, followed by 75 mg/d) [Grade 1A]. For NSTEMI ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A). We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B). For all patients presenting with NSTEMI ACS, we recommend anticoagulation with UFH or LMWH or bivalirudin or fondaparinux over no anticoagulation (Grade 1A). For NSTEMI ACS patients who will undergo an early invasive strategy of management, we recommend UFH (with a GP IIb/IIIa inhibitor) over either LMWH or fondaparinux (Grade 1B). For NSTEMI ACS patients in whom an early conservative or a delayed invasive strategy of management is to be used, we recommend fondaparinux over enoxaparin (Grade 1A) and LMWH over UFH (Grade 1B). We recommend continuing LMWH during PCI treatment of patients with NSTEMI ACS when it has been started as the "upstream" anticoagulant (Grade 1B). In low- to moderate-risk patients with NSTEMI ACS undergoing PCI, we recommend either bivalirudin with provisional ("bail-out") GP IIb/IIIa inhibitors or UFH plus a GP IIb/IIIa inhibitor over alternative antithrombotic regimens (Grade 1B). (*CHEST* 2008; 133:670S–707S)

Key words: acute coronary syndromes; anticoagulants; antiplatelet therapies; myocardial infarction

Abbreviations: ACS = acute coronary syndrome; ACT = activated clotting time; ADP = adenosine diphosphate; AMI = acute myocardial infarction; APTT = activated partial thromboplastin time; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; DTI = direct thrombin inhibitor; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; HR = hazard ratio; GP = glycoprotein; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NSTEMI = non-ST-segment elevation; NSTEMI = non-ST-segment elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and GP IIb/IIIa Inhibitors; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina; UFH = unfractionated heparin

Recommendations for Antiplatelet Therapies:

1. For all patients presenting with NSTEMI ACS, without a clear allergy to aspirin, we recommend immediate aspirin (162 to 325 mg po) and then daily oral aspirin (75 to 100 mg) [Grade 1A].
2. For all NSTEMI ACS patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300 mg po bolus, followed by 75 mg/d indefinitely (Grade 1A).
3. For NSTEMI ACS patients who are at moderate or greater risk (eg, ongoing chest pain, hemodynamic instability, positive troponin, or dynamic ECG changes) for an ischemic event and who will undergo an early invasive management strategy (ie, diagnostic catheterization followed by anatomy-driven revascularization):
 - a. We recommend "upstream" treatment either with clopidogrel (300 mg po bolus, followed by 75 mg/d) or a small-molecule IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A].
 - b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2A). Scrupulous attention to weight- and renal-based dosing algorithms must be part of eptifibatide or tirofiban administration.
 - c. For patients presenting with NSTEMI ACS, we recommend against abciximab as initial treatment except when coronary anatomy is known and PCI is planned within 24 h (Grade 1A).
4. For NSTEMI ACS patients who are at moderate or greater risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used:

a. We recommend upstream treatment with clopidogrel (300 mg oral bolus, followed by 75 mg/d) [Grade 1A].

b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2B).

5. For NSTEMI ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A).

a. We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B).

b. If ticlopidine is given, we suggest that a loading dose of 500 mg be given at least 6 h before planned PCI (Grade 2C).

c. For PCI patients who cannot tolerate aspirin, we suggest that the loading dose of clopidogrel (600 mg) or ticlopidine (500 mg) be given at least 24 h prior to planned PCI (Grade 2C).

d. We recommend use of a GP IIb/IIIa antagonist (abciximab or eptifibatide) [Grade 1A] for all NSTEMI ACS patients with at least moderate risk features undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started "upstream." We recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12-h infusion at a rate of 10 µg/min (Grade 1A) and eptifibatide as a double bolus (each 180 µg/kg, given 10 min apart) followed by an 18-h infusion of 2.0 µg/kg/min (Grade 1A). Appropriate dose reduction of eptifibatide must be based on renal function.

e. In patients undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream, we recommend against the use of tirofiban as an alternative to abciximab (Grade 1B).

6. For NSTEMI ACS patients who have received clopidogrel and are scheduled for coronary bypass surgery, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).

Recommendations for Anticoagulant Therapies

1. For all patients presenting with NSTEMI ACS, we recommend anticoagulation with UFH or LMWH or bivalirudin or fondaparinux over no anticoagulation (Grade 1A).

a. We recommend weight-based dosing of UFH and maintenance of the APTT between 50 and 70 s (Grade 1B).

b. We recommend against routine monitoring of the anticoagulant effect of LMWH (Grade 1C). Careful attention is needed to appropriately adjust LMWH dose in patients with renal insufficiency.

2. For NSTEMI ACS patients who will undergo an

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Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0691

early invasive strategy of management (*ie*, diagnostic catheterization followed by anatomy-driven revascularization):

a. We recommend UFH (with a GP IIb/IIIa inhibitor) over either LMWH or fondaparinux (Grade 1B).

b. We suggest bivalirudin over UFH in combination with a thienopyridine as an initial antithrombotic strategy in patients with moderate- to high-risk features presenting with a NSTEMI ACS and scheduled for very early coronary angiography (< 6 h) [Grade 2B].

3. For NSTEMI ACS patients in whom an early conservative or a delayed invasive strategy of management is to be used:

a. We recommend fondaparinux over enoxaparin (Grade 1A). For patients treated with upstream fondaparinux and undergoing PCI, we recommend that additional IV boluses of UFH be given at the time of the procedure (for example, 50 to 60 U/kg) as well as additional IV doses of fondaparinux (2.5 mg if also receiving a GP IIb/IIIa inhibitor and 5 mg if not) [Grade 1B]. Additionally, PCI operators should regularly flush the catheters with UFH during the procedure as well.

b. We recommend LMWH over UFH (Grade 1B). We recommend continuing LMWH during PCI treatment of patients with NSTEMI ACS when LMWH has been started as the upstream anticoagulant (Grade 1B). If the last dose of enoxaparin was given ≤ 8 h prior to PCI, we recommend no additional anticoagulant therapy (Grade 1B). If the last dose of enoxaparin was given 8 to 12 h before PCI, we recommend a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (Grade 1B).

4. In low- to moderate-risk patients with NSTEMI ACS undergoing PCI, we recommend either bivalirudin with provisional ("bail-out") GP IIb/IIIa inhibitors or UFH plus a GP IIb/IIIa inhibitor over alternative antithrombotic regimens (Grade 1B).

Both antiplatelet and anticoagulant therapies have become mainstays in the treatment of coronary artery disease (CAD). This chapter will address the acute management of patients who present with non-ST-segment elevation (NSTEMI) acute coronary syndromes (ACS), including those undergoing percutaneous coronary intervention (PCI) as part of an initial invasive management strategy, with antithrombotic treatment. Other chapters will cover the issues of antithrombotic therapy for patients presenting with ST-segment elevation acute myocardial infarction

(AMI) ["Acute ST-Segment Elevation Myocardial Infarction"] and for primary and secondary prevention in patients with chronic CAD ("The Primary and Secondary Prevention of Coronary Artery Disease").

Interpretation of the results of the trials of antithrombotic therapies in CAD requires familiarity with the nomenclature for categorizing patients with ACS. Following the observation by DeWood et al¹ in the late 1970s that intracoronary thrombosis was a key mechanism in the pathophysiology of AMI, the focus in acute cardiovascular research throughout the 1980s and into the early 1990s centered on reperfusion therapy. Data from large trials demonstrated the importance of rapid and accurate diagnosis coupled with rapid administration of fibrinolytic therapy. This approach reduced premature deaths and therefore became incorporated into the quality assessment of the care given to these patients.

During this period of intense investigation of AMI, investigators became increasingly aware of a much larger group of patients presenting to hospitals for evaluation of acute chest pain who did not have ST-segment elevation on the initial ECG. Overview analyses from the Fibrinolytic Trialists' Collaboration showed that among patients with suspected AMI, those with ST-segment elevation or new bundle-branch block on ECG benefited from treatment with fibrinolysis, whereas those presenting initially with ST-segment depression did not.²

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb trial³ was one of the first large-scale attempts to study the entire spectrum of patients presenting with acute chest pain, stratifying the randomization on the basis of their initial ECG findings (ST-segment elevation or not). The results of this trial demonstrated that patients without ST-segment elevation represent a different population than those with ST-segment elevation. The patients without ST-segment elevation were older and more likely to be female and have more cardiac and noncardiac comorbidities than patients with ST-segment elevation.

For descriptive purposes, these patients were not being categorized on the basis of their admitting diagnosis, but rather on the diagnosis that became clear 12 to 24 h later, namely unstable angina (UA) or myocardial infarction (MI) [mostly non-Q-wave MI], the two conditions that together now make up NSTEMI ACS.

Recognition of the size and clinical importance of this neglected group of patients signaled a shift in the focus of acute cardiovascular clinical research from solely concentrating on reperfusion therapy among ST-segment elevation infarction patients to those with NSTEMI ACS. The diagnoses of UA and NSTEMI MI (NSTEMI) are made retrospectively, after a period of observation and a review of serial ECGs and cardiac enzymes. The results of these trials

Table 1—Question Definition and Eligibility Criteria for Antithrombotic Agents in NSTEMI ACS (Section: Introduction)

Section	Population	Intervention(s) or Exposure	Outcome	Methodology
1.1	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	Aspirin	Mortality MI Stroke Bleeding	RCTs
1.2	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	Thienopyridines and other P2Y ₁₂ inhibitors (ADP receptor blockers)	Composite: death, MI, stroke Ischemia Bleeding	RCTs
1.3	NSTEMI ACS	Dipyridamole	Composite: death, MI, stroke Ischemia Bleeding	RCTs
1.4	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	GP IIb/IIIa Inhibitors IV	Composite: death, MI Ischemia Bleeding	RCTs
2.1	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	UFH	Composite: death, MI Ischemia Bleeding	RCTs
2.1.1	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	Level of anticoagulation	Composite: death, MI Ischemia Bleeding	Observational studies
2.2	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	LMWHs	Composite: death, MI Ischemia Bleeding	RCTs
2.3	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	Selective factor Xa Inhibitors	Composite: death, MI Ischemia Bleeding	RCTs and observational studies
2.4	NSTEMI ACS; include patients treated medically and those undergoing catheterization with and without PCI	Direct thrombin inhibitors	Composite: death, MI Ischemia Bleeding	RCTs and observational studies

showed that these patients with NSTEMI ACS have a moderate to high risk of early adverse outcomes (2 to 4% risk of death and a 10 to 12% of MI by 30 days) and therefore, may benefit from more rapid assessment, triage, and treatment.⁴

The recently updated and revised American College of Cardiology/American Heart Association⁵ and European Society of Cardiology⁶ guidelines for managing patients with UA and NSTEMI reflect this changing nomenclature. The initial focus of the guidelines considers patients with acute ischemic symptoms as having ACS, and then further differentiates them into ACS with or without ST-segment elevation. The immediate treatment decisions then flow from this differentiation. Table 1 describes the question definition and eligibility criteria for the studies considered in each section of the recommendations that follow.

1.0 ANTIPLATELET THERAPIES

1.1 Aspirin

1.1.1 Background

The chapter by Patrono et al in this supplement describes aspirin and other antiplatelet agents. Aspirin causes irreversible inhibition of platelet cyclooxygenase, thereby preventing the formation of thromboxane A₂, a platelet aggregant and potent vasoconstrictor. Aspirin has no effect on platelet aggregation induced by other agonists and is therefore a weak platelet inhibitor. The adverse effects of aspirin are primarily related to bleeding, particularly GI, which is less common at the low dosage of 75 to 162 mg/d needed to inhibit platelet aggregation.

Clinical trials have investigated various drugs inhibiting thromboxane A₂ synthase or blocking the

thromboxane A₂ receptor, or both. Although they do not decrease prostacyclin production, they have shown no advantage over aspirin.

1.1.2 Evidence From Clinical Trials

Oral antiplatelet therapy, mainly aspirin, has been the cornerstone of acute treatment for > 15 years.⁷ Despite its biochemical limitations, aspirin profoundly reduces adverse clinical events among a broad group of patients treated for acute and chronic vascular diseases.^{8–12}

In the systematic review published by the Anti-thrombotic Trialists' Collaboration,⁸ there were 5,031 patients with unstable angina in 12 trials comparing aspirin to either placebo or no treatment. Treatment with aspirin was associated with a 46% relative odds reduction in adverse vascular events.

Most of the excess bleeding related to aspirin is GI. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study¹³ comparing clopidogrel vs aspirin in patients with chronic vascular disease, the risk of GI bleeding that led to aspirin discontinuation was 0.93%.

While the risk of side effects, particularly GI bleeding, appears to increase with increasing dose, the relationship between efficacy and aspirin dose is less certain. Analyses⁸ from the Antithrombotic Trialists' Collaboration suggested that the benefits of aspirin were consistent on a relative basis across a wide range of doses (< 160 mg/d to approximately 1500 mg/d), while other analyses by Kong et al¹⁴ suggested that the effect of aspirin is weaker at higher doses. Although a head-to-head comparison is necessary to completely resolve this issue, the bulk of available evidence suggests equivalent or even superior effectiveness at lower doses, thus clinicians can be confident in administering relatively low aspirin doses.

1.2 Thienopyridines

1.2.1 Background

Ticlopidine and clopidogrel are adenosine diphosphate (ADP) receptor antagonists that inhibit ADP-induced platelet aggregation and prolong bleeding time (see chapter by Patrono et al in this supplement). Combining platelet antagonists that have different mechanisms of action is attractive. Aspirin inhibits thromboxane A₂-mediated activation and clopidogrel inhibits ADP-mediated activation.

1.2.2 Evidence From Clinical Trials

The safety profile of ticlopidine is relatively unfavorable, with frequent GI side effects, rash, neutropenia (rarely fatal), thrombocytopenia, and liver

Table 2—ST-Segment Elevation in ACS: Randomized Trials of Thienopyridines and Other P2Y₁₂ Inhibitors (ADP Receptor blockers) Compared With Placebo; Clinical Description and Results (Section 1.2.2)*

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death, No. (95% CI)	MI/UA Pectoris, No. (95% CI)	Stroke, No. (95% CI)	Ischemia (95% CI)	Bleeding (95% CI)	Comments
CURE Trial Investigators ^{30/2001}	Clopidogrel: loading dose 300 mg po followed by 75 mg/d for 3–12 mo; Placebo matching	12,562	12 mo	Cardiovascular causes: Clopidogrel: 318 (5.1%); Placebo: 345 (5.5%) RR: 0.93 (0.79–1.08) Noncardiovascular causes: Clopidogrel: 41 (0.7%); Placebo: 45 (0.7%) RR 0.91 (0.60–1.39)	Clopidogrel: 324 (5.2%); Placebo: 419 (6.7%) RR 0.77 (0.67–0.89)	Clopidogrel: 75 (1.2%); Placebo: 87 (1.4%) RR 0.86 (0.63–1.18)	Clopidogrel: 544 (8.7%); Placebo: 587 (9.3%) RR 0.93 (0.82–1.04)	Major bleeding: Clopidogrel: 231 (3.7%); Placebo: 169 (2.7%) RR 1.38 (1.13–1.67)	CURE Trial

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

function abnormalities (rare) [Table 2]. Clopidogrel monotherapy has a much more favorable safety profile and is well tolerated, as demonstrated in the CAPRIE study¹³ of > 19,000 patients.

The benefit derived from antiplatelet therapy in patients with CAD, UA, acute MI, and previous MI is well established; additionally, the added benefit from multitargeted antiplatelet regimens, particularly among high-risk patients with NSTEMI/ACS is now clearly established.

In the Clopidogrel in Unstable Angina To Prevent Recurrent Events (CURE) trial,¹⁵ 12,562 patients with NSTEMI/ACS were randomly assigned to receive clopidogrel (300 mg immediately followed by 75 mg qd) or placebo in addition to aspirin (75 to 325 mg/d) for 3 to 12 months. The first primary outcome—a composite of death from cardiovascular causes, nonfatal MI, or stroke—occurred in 9.3% and 11.4% of patients given clopidogrel and placebo, respectively (relative risk [RR] 0.80; 95% confidence interval [CI], 0.72 to 0.90; $p < 0.001$). The compelling benefit in CURE is in reducing nonfatal MI (5.2% vs 6.7%; RR, 0.77; 95% CI, 0.67 to 0.89); weak trends (nonsignificant) suggested the possibility of small reductions in death (5.1% vs 5.5%; RR, 0.93; 95% CI, 0.79 to 1.08), and stroke (1.2% vs 1.4%; RR, 0.86; 95% CI, 0.63 to 1.18) with clopidogrel. Significantly fewer patients in the clopidogrel group experienced recurrent angina (20.9% vs 22.9%; RR, 0.91; 95% CI, 0.85 to 0.98; $p = 0.01$). The benefits of clopidogrel were consistent across a broad range of patient subsets including those with MI, ST-segment deviation, elevated cardiac biomarkers, diabetes mellitus, age > 65 years, and high-risk features. Although the absolute use of concomitant glycoprotein (GP) IIb/IIIa inhibitors was low in CURE, the treatment effect of clopidogrel was consistent among those receiving and not receiving the IV platelet inhibitors.

Major bleeding (defined as disabling hemorrhage, intraocular hemorrhage leading to visual loss, or bleeding requiring transfusion of at least 2 U of blood) was significantly more common in clopidogrel-treated patients (3.7% vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; $p = 0.001$). Life-threatening bleeding (fatal hemorrhage or causing a reduction in hemoglobin of 5 g/dL or to substantial hypotension requiring inotropic support, surgical intervention; symptomatic intracranial hemorrhage, or transfusing of ≥ 4 U of blood) was also more common, although the difference did not reach conventional levels of statistical significance (2.2% vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56). There was not an excess rate of fatal bleeding, bleeding that required surgical intervention, or hemorrhagic stroke. The number of patients

requiring transfusion of ≥ 2 U of blood was higher in the clopidogrel group (2.8% vs 2.2%, $p = 0.02$).

The rate of major bleeding with clopidogrel was higher early (within 30 days of randomization; 2.0% vs 1.5%; RR, 1.31; 95% CI, 1.01 to 1.70) and also late (> 30 days after randomization: 1.7% vs 1.1%; RR, 1.48; 95% CI, 1.10 to 1.99). Bleeding associated with coronary artery bypass grafting (CABG) was particularly high among patients receiving clopidogrel within 5 days of surgery (9.6% vs 6.3%; $p = 0.06$) but bleeding was not different between the groups when clopidogrel had been discontinued for > 5 days. Overall, the risk of minor bleeding was significantly higher in patients treated with clopidogrel (5.1% vs 2.4%; $p = 0.001$).

1.2.3 Patients Receiving Coronary Stents

Thrombosis, including both in-lab and late events, remains a major challenge among patients undergoing coronary intervention and receiving a stent. The risk of acute complications is reduced with aspirin plus a thienopyridine.^{16,17} In a randomized trial¹⁸ that included 517 high-risk patients treated with Palmaz-Schatz stents for acute MI, suboptimal angioplasty, or other “high-risk” clinical and anatomic features, patients were assigned to antiplatelet therapy (aspirin plus ticlopidine) or anticoagulant therapy (aspirin, heparin, and a vitamin K antagonist) after successful stent placement. The primary end point, a composite of cardiovascular death, MI, CABG surgery, or repeat angioplasty, occurred in 1.5% of patients given antiplatelet therapy and 6.2% of those randomized to anticoagulant treatment ($p = 0.01$).¹⁸ Subacute stent thrombosis occurred in 0.8% of patients in the antiplatelet therapy group and in 5.4% of those given anticoagulants. The Stent Anticoagulation Restenosis Study¹⁹ (STARS) randomized 1,653 lower-risk patients to aspirin alone (325 mg/d), the combination of aspirin (325 mg/d) plus ticlopidine (500 mg/d) for one month, or to aspirin (325 mg/d) plus warfarin after successful placement of a Palmaz-Schatz stent.¹⁹ The composite of death, target lesion revascularization, angiographic thrombosis, or MI at 30 days was reduced from 3.6% in patients assigned to aspirin alone and 2.7% in those assigned to aspirin plus warfarin to 0.5% in those given the combination of aspirin and ticlopidine ($p < 0.001$).¹⁹ Based on these studies, the combination of aspirin plus a thienopyridine has become the standard of care.

1.2.4 Ticlopidine vs Clopidogrel

Side effects are common with ticlopidine and the drug can cause neutropenia and thrombocytopenia. Clopidogrel is safer than ticlopidine and easier to administer. Clopidogrel also does not cause neutropenia, thereby obviating the need for blood count

monitoring. Furthermore, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are rare complications of clopidogrel.^{20,21} Finally, unlike ticlopidine, which requires twice-daily administration, clopidogrel can be given once daily.^{22–24}

A metaanalysis of randomized trials showed that compared with ticlopidine, clopidogrel was associated with a significant reduction in the incidence of major adverse cardiac events (odds ratio [OR], 0.51; $p = 0.001$) and mortality (OR, 0.44; $p = 0.001$).²⁵ The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) study²⁶ randomized 1,020 patients to clopidogrel (300-mg loading dose followed by 75 mg/d) plus aspirin (325 mg/d) or clopidogrel (75 mg/d without a loading dose) and aspirin (325 mg/d), or to ticlopidine (250 mg/d) and aspirin (325 mg/d). The primary end point, a composite of major bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug, occurred in 9.1% of patients in the ticlopidine group and 4.6% of patients in the combined clopidogrel groups (RR, 0.50; 95% CI, 0.31 to 0.81; $p = 0.005$).²⁶ Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (0.9% with ticlopidine and 1.5% and 1.2% with clopidogrel, without or with a loading dose; $p =$ not significant for all comparisons).²⁶ In another study,²⁷ 700 patients were randomly assigned to receive a 4-week course of either ticlopidine (500 mg/d) or clopidogrel (75 mg/d) in addition to aspirin (100 mg/d). The prespecified primary cardiac end point, a composite of cardiac death, urgent target vessel revascularization, angiographically documented occlusion, or nonfatal MI within 30 days, occurred in 3.1% of patients assigned to clopidogrel and in 1.7% of those given ticlopidine ($p = 0.24$). Side effects were significantly less frequent in patients given clopidogrel than in those assigned to ticlopidine (4.5% and 9.6%, respectively; $p = 0.01$). If ticlopidine is administered after stent placement, it is reasonable to restrict its use to 14 days so as to minimize the risk of hematological toxicity. In one large study²⁸ that evaluated a 14-day course of ticlopidine, the frequency of ischemic events was 0.73%, and only 0.27% of patients had possible stent thrombosis between days 15 and 30 (95% CI, 0.06 to 0.77).

1.2.5 Pretreatment With Thienopyridines Prior to PCI

Most randomized trials demonstrating the benefit of ticlopidine or clopidogrel started the drug immediately after PCI was completed. In a randomized safety trial comparing prasugrel (CS-747, LY640315), a novel thienopyridine P2Y₁₂ antagonist, with clopidogrel in 904 patients undergoing PCI, Wiviott et al²⁹

found no significant difference, as both prasugrel- and clopidogrel-treated patients had low rates of bleeding (1.7% vs 1.2%, respectively; hazard ratio [HR], 1.42; 95% CI, 0.40 to 5.08).

In PCI-CURE,³⁰ pretreatment with clopidogrel for up to 10 days prior to PCI in patients with acute coronary syndromes resulted in improved 30-day outcomes compared with no clopidogrel pretreatment. An overall beneficial effect of pretreatment with clopidogrel could not be demonstrated in patients undergoing elective stent placement. In a subset analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial (described below), however, patients pretreated with clopidogrel at least 6 h prior to PCI experienced a 38.6% RR reduction in the combined end point of death, MI, or target vessel revascularization compared with those who did not receive clopidogrel pretreatment ($p = 0.01$).³¹ Additional analysis of the CREDO trial has suggested that the benefit of pretreatment may be limited to those patients who received pretreatment with clopidogrel > 14 h prior to PCI.³²

The platelet inhibition effects of thienopyridines are delayed after drug administration, but can be achieved more rapidly by giving a loading dose. Thus, higher doses of clopidogrel (600 to 900 mg) prior to PCI may provide additional benefit compared with the conventional 300-mg loading dose.³³ A randomized trial³⁴ demonstrated that after a 600 mg loading dose of clopidogrel given > 2 h prior to PCI, patients treated with high-dose heparin (140 IU/kg) had outcomes similar to those in patients treated with abciximab and lower-dose heparin (70 IU/kg). And Montalescot et al³⁵ demonstrated a greater antiplatelet effect with a 900-mg loading dose of clopidogrel compared to 300-mg and 600-mg doses. Among patients with ACS undergoing PCI, GP IIb/IIIa blockade with abciximab did add incremental benefit with fewer ischemic complications beyond that of clopidogrel pretreatment and high-dose heparin.³⁶ It should be acknowledged that the recommendation for higher doses of clopidogrel prior to PCI is based on small-modest sized trials using biomarker end points or small trials using composite end points. While there seems to be little downside risk associated with the strategy of higher doses, equipoise does exist and a definitive clinical trial addressing this question is underway.

1.2.6 Duration of Thienopyridine Therapy After Stent Placement

Recommendations for the long-term use of dual antiplatelet therapy following coronary stenting (both bare metal and drug-eluting) are provided in

the chapter on the secondary prevention of CAD by Becker et al in this supplement.

1.2.7 Economic Implications of Clopidogrel Therapy in NSTEMI ACS

The economic considerations surrounding the use of clopidogrel therapy for secondary prevention are examined in the chapter on chronic CAD (Becker et al in this supplement). The specific clinical issue considered here is whether the benefits of this therapy are demonstrable in the earliest phase of ACS and represent good value for money in that context. Although clopidogrel is a relatively expensive medication when used over the long term, use for the acute phase of ACS does not represent a large expense relative to the other costs of ACS care. Thus, the economic question posed above is dependent primarily on the demonstration of important clinical benefits in this early phase of ACS. Specifically, is there evidence that starting clopidogrel early in ACS provides an incremental reduction in major events relative to starting therapy after the acute phase of the illness has passed (generally 1 to 4 weeks)?

Of the major clinical trials providing evidence on the effectiveness of this drug in prevention of atherosclerotic complications, only the CURE Trial enrolled patients in the acute phase (*ie*, within 24 h of symptom onset) of NSTEMI ACS.¹⁵ At 30 days, the primary outcome of death from cardiovascular causes, nonfatal MI, or stroke was reduced in the clopidogrel arm by 21% over placebo ($p = 0.003$). Evidence of benefit that included the primary end point plus refractory or severe ischemia was evident within 24 h of randomization (34% reduction). Both severe ischemia (1 per 100 treated decrease) and recurrent angina (2 per 100 treated decrease) were reduced by clopidogrel during the index hospital phase of therapy. Revascularization was also decreased during the index hospitalization with clopidogrel therapy (1.9 per 100 decrease).

In the economic analysis performed by the CURE study investigators, initial hospitalization costs were reduced in the clopidogrel arm relative to placebo by about \$240 to \$300, depending on the source of the cost weights used.³⁷ Although this analysis did not consider a scenario of treatment limited to the first 30 days following randomization, if clopidogrel costs approximately \$4/d (www.drugstore.com, accessed 4/15/07), a 30-day course would cost less at \$120 than the induced cost savings that were estimated from the empirical trial data, making this strategy both clinically superior and cost saving. By economic reckoning, any therapy that is both cheaper and clinically superior clearly should be preferred to its alternative. The only caveats to be considered relate to establishing that

patients to be treated in the future are likely to show the same patterns of benefit seen in CURE, based on their underlying risk of cardiovascular complications and the patterns of adjunctive therapies used.

1.3 Dipyridamole

The effects of dipyridamole appear to be related to an increase in platelet cyclic adenosine monophosphate. Currently, there is no evidence to support use of dipyridamole either instead of, or in addition to, aspirin and the thienopyridines in the acute treatment of patients presenting with an NSTEMI ACS.

1.4 GP IIb/IIIa Inhibitors

1.4.1 Background

Randomized trials have tested GP IIb/IIIa receptor inhibitors as arterial antithrombotics and three have gained market approval for clinical use: abciximab, a monoclonal antibody fragment; eptifibatide, a peptide inhibitor; and tirofiban, a peptidomimetic inhibitor. Abciximab and eptifibatide are indicated as adjunctive antithrombotics in patients undergoing PCI, including those with ACS, while eptifibatide and tirofiban are specifically approved for “upstream” use (started at the time of presentation or diagnosis) among patients presenting with NSTEMI ACS being treated both with and without PCI.

1.4.2 Clinical Trials

A systematic overview, using individual patient data, by Boersma et al³⁸ included all 31,402 patients presenting with NSTEMI ACS enrolled in trials of GP IIb/IIIa inhibitors randomizing ≥ 1000 patients (Table 3). Overall there was a significant 1.2% absolute decrease in the incidence of death or MI at 5 days (5.7% vs 6.9%), a highly significant 16% relative reduction in the odds of death or MI (OR, 0.84; 95% CI, 0.77 to 0.93, $p = 0.0003$) [Fig 1]. Boersma et al, in a metaanalysis of three trials³⁹ (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment [CAPTURE],⁴⁰ Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms [PRISM-PLUS],⁴¹ and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy [PURSUIT]),⁴² also demonstrated a convincing effect of the GP IIb/IIIa inhibitors on outcome in patients before they underwent coronary procedures, after they underwent coronary procedures, or in individuals who did not receive coronary procedures. More recently the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial⁴³ Investigators tested a strategy of

Table 3—RCTs of GP IIb/IIIa Inhibitors IV Compared With Placebo: Clinical Description and Results (Section 1.4.2)*

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death, No./Total (95% CI)	MI/UA Pectoris, No./Total (95% CI)	Composite Death or MI, No./Total (95% CI)	Ischemia, No./Total (95% CI)	Major Bleeding†, No./Total (95% CI)	Comments
Abciximab									
CAPTURE Investigators ^{40/} 1997	Abciximab 0.25 mg/kg followed by 10 µg/min infusion; Placebo	1,265; Abciximab: 630 Placebo: 635	6 mo	30 d: Abciximab: 6/630 (0.95%) Placebo: 8/635 (1.30%) RR: 0.76 (0.26, 2.17)	30 d: Abciximab: 30/630 (4.8%) Placebo: 57/635 (9.0%) RR: 0.53 (0.35, 0.81)	30 d: Abciximab: 1/630 (0.2%) Placebo: 3/635 (0.5%) RR: 0.34 (0.04, 3.22)	Not reported	30 d: Abciximab: 24/630 (3.4%) Placebo: 12/635 (1.9%) RR: 2.02 (1.02, 4.00)	CAPTURE—study discontinued after the interim analysis of 1,050 patients; major bleeds defined as intracranial bleeding or episodes associated with a decrease in hemoglobin > 3.5 mmol/L
GUSTO IV:									
Ottervanger et al ^{14/2004}	Abcix 48: 0.25 mg/bolus followed by 0.125 µg/kg/min infusion	7,800; Abcix 48: 2,612	1 yr	30 d: Abcix 48: 111/2,612 (4.3%)	30 d: MI Abcix 48: 153/2,612 (5.9%)	30 d: Abcix 48: 238/2,612 (9.1%)	Not reported	Abcix 48: 48/2,612 (1.8%) Abcix 24: 26/2,590 (1.0%) Placebo: 24/2,598 (0.9%) RR: 1.54 (0.97, 2.43)	GUSTO IV-ACS used the TIMI criteria to classify bleeding as major, minor or insignificant
Lenderink et al ^{14/2004}	µg/kg/min infusion up to a maximum of 10 µg/min for 48 h; Placebo	Abcix 24: 2,590		Abcix 24: 88/2,590 (3.4%)	Abcix 24: 146/2,590 (5.6%)	Abcix 24: 212/2,590 (8.2%)			
James et al ^{14/2004}	Abcix 24: 0.25 mg/bolus followed by 0.125 µg/kg/min infusion up to a maximum of 10 µg/min for 24 h; Placebo	Placebo: 2,598		Placebo: 102/2,598 (3.9%)	Placebo: 133/2,598 (5.1%)	Placebo: 209/2,598 (8.0%)			
GUSTO IV Investigators ^{54/} 2001; Merlini et al ^{14/2001}				Abciximab vs Placebo: RR: 0.97 (0.77, 1.23) 1 yr: 649/7,496 (8.7%)	Abciximab vs Placebo: RR: 1.12 (0.92, 1.37)	Abciximab vs Placebo: RR: 1.08 (0.92, 1.26)			
Eptifibatide									
Pursuit Trial Investigators ^{42/} 1998; McClure et al ^{14/7/1999}	HD: Eptifibatide: 180 µg/kg bolus followed 2.0 µg/kg/min infusion; LD: Eptifibatide: 180 µg/kg bolus + 1.3 µg/kg/min infusion; Placebo: 10,948	10,948; HD: 4,722 LD: 1,487 Placebo: 4,739	30 d	At 7 d: HD: 71/4,722 (1.56%) Placebo: 95/4,739 (2.0%) RR: 0.75 (0.56, 1.02)	30 d	At 5 d (some results taken from the Boersma metaanalysis ⁵³): HD: 404/4,722 (8.6%) LD: 117/1,487 (7.9%) Placebo: 480/4,739 (10.1%) RR: 0.83 (0.74, 0.93)	Lower dose with bolus 180 µg/kg followed by an infusion of 1.3 µg/kg/min was dropped after first 3,218 patients)		
Kleiman et al ^{14/8/2000} _a		1,151 (12.2% of all PURSUIT patients)		At 30 d: HD: 165/4,722 (3.5%) Placebo: 175/4,739 (3.7%) RR: 0.95 (0.77, 1.17)		At 30 d (some results taken from the Boersma metaanalysis ⁵³): HD: 672/4,722 (14.2%) LD: 200/1,487 (13.4%) Placebo: 745/4,739 (15.7%) RR: 0.89 (0.82, 0.98)			
Kleiman et al ^{14/9/2000} _b									
Ronner et al ^{19/2002} ; Labinaz et al ^{51/2002} ; Boersma et al ^{153/2002}									

Table 3—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death, No./Total (95% CI)	MI/UA Pectoris, No./Total (95% CI)	Composite Death or MI, No./Total (95% CI)	Ischemia, No./Total (95% CI)	Major Bleeding, No./Total (95% CI)	Comments
Labinaz et al ^{132/2004}	10.948; Eptifibatide bolus 180 µg/kg followed by an infusion of 2.0 µg/kg/min Placebo bolus and infusion	1,151 (12% of all Pursuit patients); Eptifibatide: 555; Placebo: 596	6 mo	Eptifibatide 14/555 (2.5%); Placebo: 14/596 (2.3%); RR: 1.07 (0.52, 2.23); 180 d: Eptifibatide 21/555 (3.8%); Placebo: 23/596 (3.9%); RR: 0.98 (0.55, 1.75)	Eptifibatide 60/555 (10.8%); Placebo: 87/596 (14.6%); RR: 0.74 (0.54, 1.01) 180 d: Eptifibatide 67/555 (12.0%); Placebo: 101/596 (17.0%); RR: 0.71 (0.53, 0.95)	Not reported	Eptifibatide 30/555 (5.4%); Placebo: 40/596 (6.7%); RR: 0.81 (0.51, 1.27)	Major bleeding: Eptifibatide: 39/555 (7.1%); Placebo: 27/596 (4.5%); RR: 1.55 (0.96, 2.50)	PURSUIT trial subset of those with balloon angioplasty
Lamifiban PARAGON Investigators ^{154/1998} ; Moliterno et al ^{155/2000}	HD + Hep: high-dose lamifiban 750 µg bolus followed by an infusion of 5.0 µg/min HD; no Hep: high-dose lamifiban 750 µg bolus + heparin placebo; LD+Hep: low-dose lamifiban 300 µg bolus followed by an infusion of 1.0 µg/min heparin; LD no Hep: low-dose lamifiban 300 µg bolus + heparin placebo; Control: placebo + heparin	2,282; HD + Hep: 373; HD, no Hep: 396; LD + Hep: 377; LD, no Hep: 378; Control: 758	1 yr	At 30 d: HD + Hep: 14/373 (3.8%); HD no Hep: 14/396 (3.5%); LD+Hep: 11/377 (2.9%); LD, no Hep: 12/378 (3.2%); Control: 22/758 (2.9%); RR lamifiban vs control: 1.15 (0.70, 1.89); At 6 mo: HD+Hep: 28/373 (7.6%); HD, no Hep: 24/396 (6.1%); LD + Hep: 18/377 (4.8%); LD, no Hep: 21/378 (5.6%); Control: 50/758 (6.6%); RR lamifiban vs control: 0.91 (0.65, 1.26)	At 30 d: HD + Hep: 42/373 (11.3%); HD no Hep: 42/396 (10.6%); LD+Hep: 35/377 (9.3%); LD, no Hep: 36/378 (9.5%); Control: 80/758 (10.6%); RR lamifiban vs control: 0.96 (0.75, 1.24); At 6 mo: HD+Hep: 52/373 (13.9%); HD, no Hep: 48/396 (12.0 %); LD + Hep: 40/377 (10.5%); LD, no Hep: 42/378 (11.1%); Control: 108/758 (14.3%); RR lamifiban vs control: 0.90 (0.70, 1.13)	At 30 d: HD + Hep: 46/373 (11.6%); HD no Hep: 46/396 (12.3%); LD + Hep: 41/377 (10.8%); LD, no Hep: 39/378 (10.3%); Control: 89/758 (11.7%); RR lamifiban vs control: 0.96 (0.76, 1.22)	Not reported	At 30 d: HD + Hep: 9/373 (2.4%); HD no Hep: 5/396 (1.3%); LD + Hep: 2/377 (0.5%); LD, no Hep: 3/378 (0.8%); Control: 6/758 (0.8%); RR lamifiban vs Control: 0.75 (0.27, 2.10)	PARAGON-A: all numbers estimated from percentages presented in this chapter

Table 3—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death, No./Total (95% CI)	MI/UA Pectoris, No./Total (95% CI)	Composite Death or MI, No./Total (95% CI)	Ischemia, No./Total (95% CI)	Major Bleeding†, No./Total (95% CI)	Comments
Newby et al ⁶⁹ /2001	Lamifiban: 500 µg I/V lamifiban bolus, adjusted dose ≤ 72 h; Placebo: 500 µg I/V bolus, adjusted dose ≤ 72 h	1,160; Lamifiban: 571; Placebo: 586	Primary efficacy end point 30 d	TnT positive: Lamifiban: 7/227 (3.1%); Placebo: 12/237 (5.1%); RR: 0.61 (0.24, 1.52); TnT negative: Lamifiban: 4/344 (1.2%); Placebo: 7/349 (2.0%); RR: 0.58 (0.17, 1.96)	TnT positive: Lamifiban: 21/227 (9.3%); Placebo: 41/237 (17.3%); RR: 0.53 (0.33, 0.88); TnT negative: Lamifiban: 32/344 (9.3%); Placebo: 34/349 (9.7%); RR: 0.95 (0.60, 1.51)	Stroke: TnT positive: Lamifiban: 4/227 (1.8%); Placebo: 1/237 (0.4%); RR: 4.18 (0.47, 37.08); TnT negative: Lamifiban: 4/344 (1.2 %); Placebo: 0/349 (0%); RR: 9.15 (0.49, 168.95)	TnT positive: Lamifiban: 1/227 (0.4%); Placebo: 1/237 (0.4%); RR: 2.09 (0.19, 22.87); TnT negative: Lamifiban: 3/344 (0.9%); Placebo: 2/349 (0.6%); RR: 1.52 (0.26, 9.05)	PARAGON-B Troponin T Trial	
PARAGON-B Investigators ⁶⁸ /2002	Lamifiban: 500 µg I/V lamifiban bolus followed by adjusted-dose infusion ≤ 72 h; Placebo	Lamifiban: 2,628; Placebo: 2,597	Primary efficacy end point 30 d	At 30 d: Lamifiban: 752/600 (2.9%); Placebo: 852/569 (3.3%); RR: 0.87 (0.64, 1.18)	At 30 d: Lamifiban: 229/2600 (8.8%); Placebo: 252/2,569 (9.8%); RR: 0.90 (0.76, 1.06)	At 30 d: Lamifiban: 278/2,628 (10.6%); Placebo: 296/2,597 (11.4%); RR: 0.93 (0.80, 1.08)	At 30 d: Lamifiban: 392/600 (1.5%); Placebo: 392/569 (1.5%); RR: 0.99 (0.64, 1.53)	At 30 d: Lamifiban: 34/2594 (1.3%); Placebo: 232/564 (0.9%); RR: 1.46 (0.86, 2.47)	PARAGON-B Trial
Tirofiban									
PRISM + Investigators ⁴¹ /1998	Tirofiban + heparin: tirofiban 0.4 µg/kg/min for 30 min followed by an infusion of 0.1 µg/kg/min + adjusted-dose heparin;	1,031; Tirofiban + heparin: 336; Tirofiban: 345; Heparin: 350	6 mo	48 h: tirofiban + heparin: 0/336; Tirofiban: 2/345 (0.6%); Heparin: 1/350 (0.3%); RR: 1.30 (0.09, 11.30); At 7 d: Tirofiban + heparin: 5/336 (1.5%); Tirofiban: 16/345 (4.6%); Heparin: 4/350 (1.1%); RR: 4.82 (1.67, 13.91); At 30 d: Tirofiban + heparin: 7/336 (2.1%); Tirofiban: 21/345 (6.1%); Heparin: 14/350 (4.0%); RR: 1.84 (0.98, 3.43); At 6 mo: Tirofiban + heparin: 17/336 (5.1%); Tirofiban: 25/345 (7.2%); Heparin: 24/350 (6.9%); RR: 1.61 (0.99, 2.60)	48 h: Tirofiban + heparin: 2/336 (0.6%); Tirofiban: 5/345 (1.4%); Heparin: 6/350 (1.7%); RR: 0.60 (0.2, 1.77); At 7 d: Tirofiban + heparin: 9/336 (2.7%); Tirofiban: 24/345 (7.0%); Heparin: 25/350 (7.1%); RR: 1.21 (0.74, 2.0); At 30 d: Tirofiban + heparin: 19/336 (5.7%); Tirofiban: 31/345 (9.0%); Heparin: 32/350 (9.1%); RR: 1.44 (0.94, 2.18); At 6 mo: Tirofiban + heparin: 26/336 (7.7%); Tirofiban: 35/345 (10.1%); Heparin: 37/350 (10.6%); RR: 1.51 (1.03, 2.22)	48 h: Tirofiban + heparin: 19/336 (5.7%); Tirofiban: 26/345 (7.5%); Heparin: 24/350 (6.9%); RR: 0.96 (0.60, 1.55); At 7 d: Tirofiban + heparin: 39/336 (11.6%); Tirofiban: 59/345 (17.1%); Heparin: 59/350 (16.9%); RR: 1.53 (1.14, 2.04); At 30 d: Tirofiban + heparin: 63/336 (18.8%); Tirofiban: 81/345 (23.5%); Heparin: 78/350 (22.3%); RR: 1.70 (1.34, 2.14); At 6 mo: Tirofiban + heparin: 98/336 (29.2%); Tirofiban: 105/345 (30.4%); Heparin: 110/350 (31.4%); RR: 0.82 (0.65, 1.03)	The outcome events mentioned are before the discontinuation of the study in the tirofiban-only group		

Table 3—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death, No./Total (95% CI)	MI/UA Pectoris, No./Total (95% CI)	Composite Death or MI, No./Total (95% CI)	Ischemia, No./Total (95% CI)	Major Bleeding†, No./Total (95% CI)	Comments
PRISM Investigators ⁶⁰ 1998	Tirofiban; 0.6 µg/kg bolus + 0.15 µg/kg/min infusion + placebo heparin; Heparin + placebo	3,232; Tirofiban: 1,616; Heparin: 1,616	6 mo	At 48 h: Tirofiban: 6/1,616 (0.4%) Heparin: 3/1,616 (0.2%) RR: 0.76 (0.42, 1.39); At 7 d: Tirofiban: 16/1,616 (1.0%) Heparin: 36/1,616 (1.6%); RR: 0.63 (0.34, 1.18); At 30 d: Tirofiban: 37/1,616 (2.3%) Heparin: 58/1,616 (3.6%) RR: 0.62 (0.41, 0.93)	At 48 h: Tirofiban: 15/1,616 (0.9%) Heparin: 23/1,616 (1.4%) RR: 0.64 (0.33, 1.25); At 7 d: Tirofiban: 42/1,616 (2.6%) Heparin: 50/1,616 (3.1%) RR: 0.84 (0.56, 1.26); At 30 d: Tirofiban: 66/1,616 (4.1%) Heparin: 69/1,616 (4.3%) RR: 0.95 (0.68, 1.34)	At 48 h: Tirofiban: 61/1,616 (3.8%) Heparin: 90/1,616 (5.6%); RR: 0.67 (0.48, 0.92); At 7 d: Tirofiban: 166/1,616 (10.3%) Heparin: 181/1,616 (11.2%) RR: 0.90 (0.73, 1.11); At 30 d: Tirofiban: 257/1,616 (15.9%) Heparin: 276/1,616 (17.1%) RR: 0.92 (0.78, 1.09)	At 48 h: Tirofiban: 57/1,616 (3.5%) Heparin: 86/1,616 (5.3%) RR: 0.65 (0.46, 0.91); At 7 d: Tirofiban: 147/1,616 (9.1%) Heparin: 160/1,616 (9.9%) RR: 0.91 (0.73, 1.14); At 30 d: Tirofiban: 171/1,616 (10.6%) Heparin: 175/1,616 (10.8%) RR: 0.98 (0.79, 1.21)	Tirofiban: 6/1,616 (0.4%) Heparin: 6/1,616 (0.4%) RR: 1.00 (0.32, 3.09)	PRISM-PLUS Study

*Abcix = abciximab; Abcix 48 = abciximab bolus plus 48-h infusion; Abcix 24 = abciximab bolus plus 24-h infusion; NoP = no prophylaxis; NR = not reported; HD = high dose; LD = low dose; Hep = heparin. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

†Major bleeding: overt bleeding resulting either in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop ≥ 3 g/dL; or the requirement of transfusion of ≥ 2 U of blood (TIMI criteria).

upstream vs delayed (reserved for PCI) GP IIb/IIIa inhibitor administration. While there was less major bleeding associated with the delayed usage (4.9% vs 6.1%, $p = 0.009$), this strategy was not shown to be noninferior to an upstream usage strategy with regard to the ischemic composite of 30 day death, MI or unplanned revascularization for ischemia (7.9% vs 7.1%; RR, 1.12; 95% CI, 0.97 to 1.29; $p = 0.044$). An ongoing, large randomized clinical trial⁴⁴ is testing the benefit of very early upstream eptifibatide vs selective usage of this agent in the catheterization laboratory at the time of PCI.

1.4.2.1 Abciximab

Abciximab was first studied in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) Trial, which included 2,099 high-risk patients undergoing PCI.⁴⁵ All patients received aspirin (325 mg) and a non-weight-adjusted heparin bolus (10,000–12,000 IU) prior to PCI. Patients were then randomly assigned to treatment with placebo, a bolus of abciximab (0.25 mg/kg), or the same bolus dose of abciximab followed by a 12-h abciximab infusion (10 µg/min). Compared with placebo, bolus plus infusion abciximab was associated with a 35% reduction in frequency of the end point, a composite of death, nonfatal MI, need for repeat revascularization, or procedural failure (12.8% and 8.3%, respectively; $p = 0.008$).⁴⁵ However, major bleeding complications were twice as frequent in patients receiving abciximab, reflecting the high dose of heparin that was given in this study.

The Evaluation of PTCA to Improve Long-Term Outcome by Abciximab GP IIb/IIIa Blockade (EPILOG) Trial⁴⁶ included 2792 low-risk patients undergoing PCI. All patients received aspirin and were then randomized to weight-adjusted heparin (100 IU/kg with target activated clotting time [ACT] of 300 s) plus placebo; the same heparin dose plus abciximab; or lower-dose heparin (70 IU/kg with minimum ACT target of 200 s) plus abciximab. Compared with placebo, the 30-day end point, a composite of death, MI, or urgent revascularization, was significantly lower in patients treated with abciximab plus lower-dose or usual-dose heparin (11.7%, 5.2%, and 5.4%, respectively; $p < 0.001$). The need for transfusion was 3.9% in patients given the usual heparin dose plus placebo, whereas it was 3.3% and 1.9% in the abciximab-treated patients given usual-dose or low-dose heparin, respectively. Based on these results, the use of a lower-dose heparin regimen became the standard of care.

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT)⁴⁷ trial randomly assigned 2,399 patients with ischemic coronary artery disease to stenting plus placebo, stenting plus abciximab, or balloon PTCA plus

abciximab. The primary 30-day end point, a combination of death, MI, or need for urgent revascularization, occurred in 10.8% of patients in the stent plus placebo group, 5.3% of those in the stent plus abciximab group (HR 0.48; $p < 0.001$), and 6.9% in the group undergoing balloon angioplasty and given abciximab (HR, 0.63; $p = 0.007$). No significant differences in bleeding complications were noted among the various treatment groups.

The effect of periprocedural abciximab on the prevention of late restenosis has been controversial. Although the EPIC study⁴⁸ showed a 23% reduction in cumulative 6 month clinical events ($p = 0.001$), these events were primarily related to the prevention of early (< 30 day) periprocedural events. A subgroup of diabetic patients undergoing stent implantation in EPISTENT showed a reduction in 6-month target vessel revascularization from 16.6% in those receiving placebo to 8.1% in those receiving abciximab.⁴⁹ Subsequent studies failed to demonstrate an effect of abciximab on reducing restenosis risk.⁵⁰

Abciximab does not reduce complication rates associated with saphenous venous graft interventions.⁵¹ Although “bailout” abciximab is often given during or just after PCI if there is residual dissection, thrombus, or suboptimal results,⁵² this approach has not been evaluated in prospective studies.

Late mortality benefits have been reported after use of abciximab.⁵³ In a metaanalysis of 12 trials that enrolled 20,186 patients, 30-day mortality was significantly reduced with GP IIb/IIIa inhibition (OR, 0.73; 95% CI, 0.55 to 0.96; $p = 0.024$).⁵³ At 6 months, the OR was 0.84 (95% CI, 0.69 to 1.03; $p = 0.087$).⁵³

The Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes (GUSTO IV-ACS) trial⁵⁴ enrolled 7825 patients presenting with ischemic symptoms and either biomarker or ECG evidence of myocardial infarction/ischemia. Patients were randomized to one of three treatment groups, in addition to receiving heparin or aspirin: placebo, abciximab bolus plus 24-h infusion, or abciximab bolus plus 48-h infusion.⁵⁴ Patients were treated conservatively without early cardiac catheterization. The primary end point was the 30-day composite of death and MI. At 30 days, there were no significant differences among the treatment groups with regard to the primary efficacy composite, but abciximab was associated with a fivefold-increased risk in major bleeding (1.0% vs 0.2%) and an increased risk of thrombocytopenia.

1.4.2.2 Eptifibatide

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) Trial⁵⁵ enrolled 4,010 patients undergoing PCI. Patients were randomized to treatment with placebo, a low-dose bolus of

eptifibatide (135 $\mu\text{g/kg}$) followed by a low-dose infusion (0.5 $\mu\text{g/kg/min}$ for 20 to 24 h), or the same eptifibatide bolus and a slightly higher-dose infusion (0.75 $\mu\text{g/kg/min}$ for 20 to 24 h). The primary end point, a 30-day composite of death, MI, unplanned CABG or repeat PCI, or coronary stenting for abrupt closure, occurred in 11.4% of patients in the placebo group compared with 9.2% in the 135/0.5 eptifibatide group ($p = 0.063$) and 9.9% in the eptifibatide 135/0.75 group ($p = 0.22$).⁵⁵ Eptifibatide treatment did not increase rates of major bleeding or transfusion.

It is now recognized that the eptifibatide dose used in the IMPACT-II Trial was insufficient to provide adequate platelet GP IIb/IIIa inhibition during PCI. The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) study⁵⁶ evaluated a higher-dose, double-bolus, eptifibatide regimen (two 180 $\mu\text{g/kg}$ boluses given 10 min apart followed by an infusion of 2.0 $\mu\text{g/kg/min}$ for 18 to 24 h) vs placebo in a randomized study of 2,064 patients undergoing stent implantation in a native coronary artery.⁵⁶ The primary end point, a composite of death, MI, urgent target vessel revascularization, or bailout GP IIb/IIIa inhibitor therapy within 48 h of randomization, occurred in 10.5% of 1,024 patients given placebo and in 6.6% of those treated with eptifibatide a risk ratio of 0.63 (95% CI, 0.47 to 0.84; $p = 0.0015$). The 30-day end point of death or MI was also reduced, from 10.5% in placebo-treated patients to 6.8% in eptifibatide-treated patients, a risk ratio of 0.65 (95% CI, 0.49 to 0.87; $p = 0.0034$). These effects were sustained 1 year after the procedure, and eptifibatide was also effective in the subgroup of high-risk diabetic patients.⁵⁷ Major bleeding was infrequent, but occurred more frequently with eptifibatide than with placebo (1.0% and 0.4%, respectively; $p = 0.027$).⁵⁶ Based on the results of this trial, the eptifibatide regimen used in the ESPRIT trial has become the standard of care.

The large international Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial⁴² enrolled 10,948 patients presenting with a NSTEMI/ACS and randomized to one of three drug regimens on a background of aspirin and unfractionated heparin (UFH): eptifibatide 180 $\mu\text{g/kg}$ bolus followed by an infusion of either 2.0 or 1.3 $\mu\text{g/kg-min}$ or placebo bolus plus infusion. The primary end point was the composite of death and nonfatal MI at 30 days. Since neither dose of eptifibatide had yet been studied in randomized clinical trials, the study was designed to drop the lower dose if the high dose appeared to have an acceptable bleeding profile after approximately 1,000 patients had been enrolled per treatment group. In the primary analysis of high-dose vs

placebo, eptifibatide reduced the 30-day composite from 15.7 to 14.2% ($p = 0.042$), a RR reduction of 9.6%.⁴² The benefit was maintained at 6 months. Bleeding was increased overall among the treated patients, with GUSTO moderate or severe bleeding occurring at a rate of 12.8% among eptifibatide patients compared with 9.9% among placebo patients (RR, 1.3; 95% CI, 1.1 to 1.4). This bleeding difference was confined to patients not undergoing CABG. There was a significant increase in thrombocytopenia among the patients treated with the platelet inhibitor.⁵⁸ There was no increase in the risk of intracranial hemorrhage among those treated with eptifibatide.

1.4.2.3 Tirofiban

Two moderate-size trials have evaluated tirofiban in an NSTEMI ACS population: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)⁵⁹ and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS).⁶⁰ The PRISM trial randomized 3231 patients presenting with ACS to either tirofiban (loading dose of 0.6 $\mu\text{g}/\text{min}$ for 30 min followed by 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 47.5 h) or heparin.⁵⁹ The drugs were to be given for 48 h and cardiac catheterization was to be deferred until the study drug was discontinued. The 48-h primary composite of death, MI, or refractory ischemia was reduced with tirofiban from 5.6 to 3.8% with heparin ($p = 0.01$). The absolute benefit of tirofiban was maintained through 30 days, although the relative benefit was lessened, as additional events accrued in both treatment arms after discontinuation of the therapy. Both groups had a 0.4% incidence of major bleeding.

In the PRISM-PLUS trial,⁶⁰ 1,915 patients were randomized to treatment with tirofiban alone, tirofiban with heparin, or heparin alone. The primary end point was the composite of death, MI, or refractory ischemia at 7 days. During an interim review by the Data Safety and Monitoring Board, the tirofiban-alone arm was dropped due to excess mortality at 7 days. The trial continued with the remaining two treatment arms. Tirofiban plus heparin was associated with a significant reduction in the primary composite end point compared with heparin alone (12.9% vs 17.9%, $p = 0.004$). This benefit was maintained at 30 days and 6 months. Thrombolysis in Myocardial Infarction (TIMI) major bleeding was not significantly increased among the non-CABG patients (1.4% vs 0.8%, $p = 0.23$).

Like the other GP IIb/IIIa inhibitors, tirofiban also has been evaluated in patients undergoing PCI. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial,⁶¹ enrolled 2,139

patients undergoing PCI within 72 h of experiencing ACS. After pretreatment with aspirin and heparin, patients were randomized to receive tirofiban (bolus of 10 $\mu\text{g}/\text{kg}$ followed by an infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ > 36 h) or placebo. The primary 30-day end point, a composite of death, MI, CABG, repeat angioplasty for recurrent ischemia, or stent insertion for abrupt closure, was a nonsignificant 16% lower with tirofiban treatment than with placebo ($p = 0.161$).⁶¹ Major bleeding occurred in 5.3% of those given tirofiban and in 3.7% of those randomized to placebo ($p = 0.096$).

In a larger study,⁶² 4,809 patients destined for coronary stent placement were randomly assigned to receive either the same dose of tirofiban used in the RESTORE trial or abciximab prior to the procedure. The primary end point, a composite of death, nonfatal MI, or urgent target vessel revascularization at 30 days, occurred more frequently in the tirofiban group than in the abciximab group (7.6% and 6.0%, respectively; $p = 0.038$). The relative benefit of abciximab was consistent regardless of age, sex, the presence or absence of diabetes, or the presence or absence of pretreatment with clopidogrel.⁶² Subsequent studies have suggested that the bolus dose of tirofiban given in this study may have been suboptimal.^{63–66} Supporting this concept, larger tirofiban bolus doses have been shown to produce more inhibition of platelet aggregation than lower doses.⁶⁷ Based on the results of the studies done with tirofiban to date, this agent is not recommended in the PCI setting.

1.4.3 Broad Drug-Class Issues to Consider With GP IIb/IIIa Inhibitors

Three trials, PARAGON B,⁶⁸ PRISM,⁵⁹ and CAPTURE⁴⁰ have reported a preferential treatment effect of GP IIb/IIIa inhibitors among NSTEMI ACS patients who present with elevated troponin levels. Newby et al⁶⁹ have shown that there is a strong treatment interaction, suggesting that the effect among troponin-positive patients is substantially larger than in troponin-negative patients (in whom there might be no benefit at all).

Part of the reason for the recommendations that this class of drugs should be used in moderate- to high-risk patients is their value as part of an invasive strategy.^{5,70} None of the six large randomized trials specifically addressed the issue of whether the GP IIb/IIIa inhibitors add incremental value to medical therapy without PCI or CABG by randomizing an appropriate group of patients. Inappropriate analysis of postrandomization subgroups (*ie*, PCI subgroups that accrue after randomization and thus are subject to bias) suggested that the GP IIb/IIIa inhibitors preferentially benefit patients undergoing percutaneous procedures more than those not undergoing

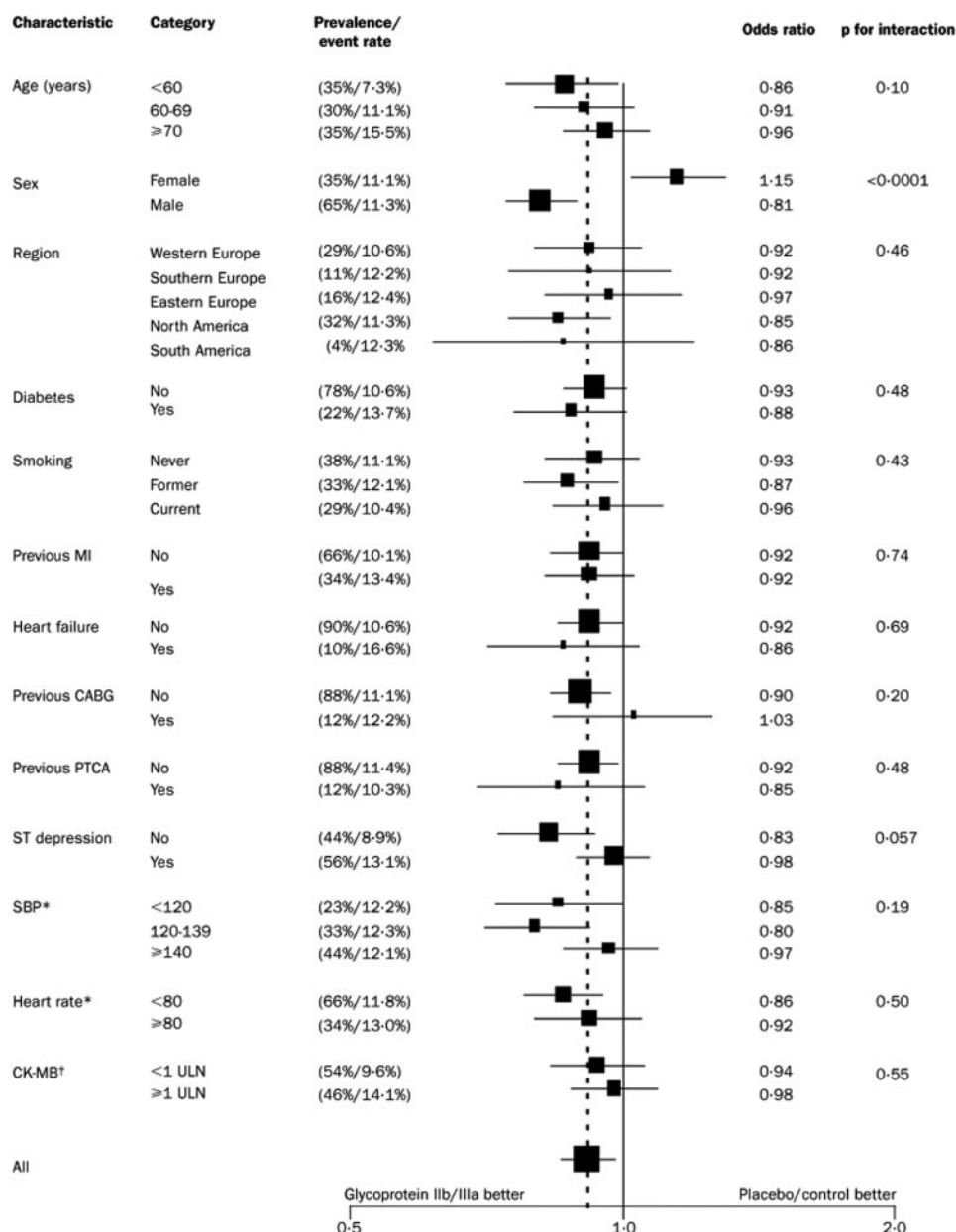


FIGURE 1. Systematic overview of GP IIb/IIIa inhibitor trials among patients presenting with NSTEMI ACS. This shows the major subgroups at baseline. PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic BP; CK = creatine kinase; ULN = upper limit of normal. Reprinted with permission from Elsevier (*The Lancet* 2002; 359:189–198).

such procedures.⁷¹ Two important issues help to clarify this controversy. First, at the time of presentation, it is challenging to predict which specific patients will have PCI or CABG based on clinical characteristics alone.⁷² It is knowledge of the coronary anatomy gained from a diagnostic cardiac catheterization that dictates revascularization strategy. Second, although the evidence suggests that an early invasive strategy (early cardiac catheterization followed by anatomy-driven revascularization) is superior to a conservative management strategy, the

optimal timing of the early catheterization strategy is unknown. In US-based practices, where the median time to catheterization is approximately 24 h,^{73,74} there is a substantial period prior to the procedure that corresponds with the period of highest risk.

The use of multiple antithrombotic agents is complicated for this group of patients. It is clear from the trial data that GP IIb/IIIa inhibitors add clinical value on background therapy of aspirin and heparin. But the major trials of the GP IIb/IIIa inhibitors were performed prior to the completion of the

CURE trial, which itself was predominantly conducted in countries where there was a low usage of the IV platelet inhibitors. Thus, while the effect of clopidogrel, given in addition to aspirin and heparin, was consistent among the groups receiving and not receiving concomitant GP IIb/IIIa inhibitors, the incremental value of adding GP IIb/IIIa inhibitors to aspirin, heparin, and clopidogrel remains uncertain. Recommendations on the use of antiplatelet therapies therefore reflect the limitations of the trials regarding combining clopidogrel and GP IIb/IIIa inhibitors. More data are clearly needed.

Recently, Kastrati et al reported the results of the ISAR-REACT 2 trial comparing abciximab with placebo among ACS patients undergoing PCI and pretreated with clopidogrel (600 mg at least 2 h prior to the procedure).³⁶ Overall, abciximab was associated with a significant 25% risk reduction (OR, 0.75; 95% CI, 0.58 to 0.97; $p = 0.03$) in the 30-day primary composite end point of death, MI, and urgent target vessel revascularization (11.9% vs 8.9%). This effect was concentrated among the subset of patients who were troponin positive at baseline (13.1% vs 18.3% among troponin positive; 4.6% vs 4.6% among troponin negative, p for interaction = 0.07). These data suggest that there may be incremental value to adding GP IIb/IIIa inhibitors to clopidogrel among the highest risk group of NSTEMI ACS patients. More data on this issue will be forthcoming from the ongoing Early Glycoprotein IIb/IIIa Inhibition in NonST-segment Elevation Acute Coronary Syndrome (EARLY ACS) trial.⁴⁴

Bleeding has emerged as an important adverse clinical end point among NSTEMI ACS patients.^{75–77} Several observational studies have noted an adverse relationship between in-hospital major bleeding or blood transfusion and subsequent mortality, and an overview of clinical trials in mostly surgical/trauma patients suggest a deleterious effect of a liberal blood transfusion strategy compared with a conservative transfusion strategy.⁷⁸ These data suggest that avoidance of bleeding and especially of transfusion may be critical in the balance of preventing thrombosis while preserving hemostasis.⁷⁹

Recently, Alexander et al⁸⁰ have reported that overdosing of GP IIb/IIIa inhibitors is quite common among NSTEMI ACS patients. They report in a registry population of NSTEMI ACS patients admitted to US hospitals that 26.8% of patients treated with a GP IIb/IIIa inhibitor are dosed outside the recommended range, and that excessive dosing carries with it a marked increased risk of major bleeding, including blood transfusion, compared with recommended dosing (OR 1.36; 95% CI, 1.10 to 1.68). Attention to proper weight and renal function-based dosing is critical when prescribing GP IIb/IIIa inhibitors.

1.4.4 Economic Implications of IV Antiplatelet Therapy in ACS

Based on the prevailing pathophysiologic model of ACS and the demonstrated benefits of aspirin in reducing death and MI in this disorder, more powerful antiplatelet agents have been developed over the last decade that could be administered IV for rapid onset (and possibly rapid reversal) of a more potent antiplatelet effect. Abciximab, a biological antibody fragment, did not reduce clinical events relative to placebo in the GUSTO IV Trial⁵⁴ and is now used primarily in higher-risk PCI procedures, as discussed elsewhere in this supplement. Eptifibatide and tirofiban, both small molecules, have demonstrated benefit in NSTEMI ACS relative to placebo, as discussed elsewhere in this chapter.

In the PURSUIT Trial⁴² of almost 11,000 ACS patients, eptifibatide given for a median of 3 days reduced the absolute 30 day rate of death or MI by 1.5% relative to placebo ($p = 0.04$). Economic analysis of this trial from the US perspective demonstrated two important findings.⁸¹ First, with 85% of the US patients undergoing cardiac catheterization, no evidence was observed for an effect of eptifibatide on the rates of revascularization or days in the hospital. Second, given that there was no induced cost savings associated with therapy, the relevant economic question in the PURSUIT Trial is whether the incremental cost of the new treatment is reasonable relative to its incremental health benefits. In the PURSUIT Trial, each patient treated with eptifibatide had an incremental drug cost of around \$1,100 per patient, while 67 patients needed to be treated to prevent one death or MI > 30 days. The methods of cost effectiveness analysis are used to translate these empirical observations into a measure that reflects the efficiency of production of incremental health benefits with eptifibatide that can be compared with efficiency metrics from other therapies of interest. The underlying concept is that with a finite budget to spend on health care, decision makers need to know which treatment options provide the best value for money. While efficiency is clearly not the sole, or perhaps even the dominant, element in most decisions about health-care spending, informed decision making without such data is not usually possible.

In the PURSUIT Trial, translation of the observed treatment benefit of eptifibatide into the preferred metric of health benefit for cost-effectiveness analysis, incremental life-years, yielded the result that each eptifibatide patient gained 0.11 life-years relative to the placebo patients. When combined with the incremental costs of therapy, this study estimated that producing an extra life-year using eptifibatide

therapy in NSTEMI ACS cost about \$16,500. Producing an extra quality-adjusted life-year cost almost \$20,000. Using 2006 US updated pricing information for eptifibatide yields an incremental cost of around \$2,000 for the 72-h regimen. At this price, the corresponding cost-effectiveness ratio is around \$28,000 per life-year saved and \$33,000 per quality-adjusted life-year saved.

By conventional benchmarks, eptifibatide as used in the US PURSUIT cohort would be considered economically attractive or cost effective, even using the higher 2006 prices. The main determinants of this result are the cost of the eptifibatide regimen and the likelihood that any new cohort being treated will experience similar clinical benefit to that seen in the US cohort of PURSUIT. One complexity discussed elsewhere in this chapter is the difficulty in parsing out the benefit due to eptifibatide in medically treated patients vs the benefits in patients undergoing PCI.

Recommendations for Antiplatelet Therapies

1. For all patients presenting with NSTEMI ACS without a clear allergy to aspirin, we recommend immediate aspirin (162 to 325 mg po) and then daily oral aspirin (75 to 100 mg) [Grade 1A].

2. For all NSTEMI ACS patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300 mg po bolus, followed by 75 mg/d indefinitely (Grade 1A).

3. For NSTEMI ACS patients who are at moderate or greater risk (eg, ongoing chest pain, hemodynamic instability, positive troponin, or dynamic ECG changes) for an ischemic event and who will undergo an early invasive management strategy (ie, diagnostic catheterization followed by anatomy-driven revascularization):

a. We recommend upstream treatment either with clopidogrel (300 mg po bolus, followed by 75 mg/d) or a small-molecule IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A].

b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2A). Scrupulous attention to weight- and renal-based dosing algorithms must be part of eptifibatide or tirofiban administration.

c. For patients presenting with NSTEMI ACS, we recommend against abciximab as initial treatment except when coronary anatomy is known and PCI is planned within 24 h (Grade 1A).

4. For NSTEMI ACS patients who are at moderate or greater risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used:

a. We recommend upstream treatment with clopidogrel (300-mg oral bolus, followed by 75 mg/d) [Grade 1A].

b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2B).

5. For NSTEMI ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A):

a. We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B).

b. If ticlopidine is given, we suggest that a loading dose of 500 mg be given at least 6 h before planned PCI (Grade 2C).

c. For PCI patients who cannot tolerate aspirin, we suggest that the loading dose of clopidogrel (600 mg) or ticlopidine (500 mg) be given at least 24 h prior to planned PCI (Grade 2C).

d. We recommend use of a GP IIb/IIIa antagonist (abciximab or eptifibatide) [Grade 1A] for all NSTEMI ACS patients with at least moderate-risk features undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream. We recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12-h infusion at a rate of 10 µg/min (Grade 1A) and eptifibatide as a double bolus (each 180 µg/kg, given 10 min apart) followed by an 18-h infusion of 2.0 µg/kg/min (Grade 1A). Appropriate dose reduction of eptifibatide must be based on renal function.

e. In patients undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream, we recommend against the use of tirofiban as an alternative to abciximab (Grade 1B).

6. For NSTEMI ACS patients who have received clopidogrel and are scheduled for coronary bypass surgery, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).

2.0 ANTICOAGULANT THERAPIES

Pharmacologic therapies designed to attenuate thrombin generation and activity are attractive because of the critical role of thrombin in ACS.

2.1 Unfractionated Heparin

Unfractionated heparin (UFH) is a heterogeneous mixture of polysaccharide molecules (average mw 15,000 to 18,000 d) [see chapter by Hirsh et al in this supplement]. In addition to a high degree of size/

length heterogeneity, there is also a substantial amount of compositional heterogeneity. Typically one third of the molecules found within a standard pharmaceutical heparin preparation contain the pentasaccharide sequence required for antithrombin binding and anticoagulant activity.

Multiple clinical trials have compared the benefits of UFH and aspirin among patients with unstable angina and NSTEMI. A pooled analysis of the ATACS,^{82,83} RISC⁸⁴ and Thérout et al¹¹ studies yields a RR of 0.44 (95% CI, 0.21 to 0.93) for death/MI with combination aspirin and UFH therapy compared with aspirin alone.

The first trial, conducted by Thérout et al,¹¹ compared aspirin (325 mg bid), UFH (5,000-U bolus, 1,000 U/h IV), their combination, and placebo in 479 patients. It is the only study that compared UFH (alone) and aspirin (alone) as well as combination therapy. Refractory angina occurred in 8.5%, 16.5%, and 10.7% of patients, respectively (RR, 0.47 for UFH compared with aspirin; 95% CI, 0.21 to 1.05; $p = 0.06$). MI occurred in 0.9%, 3.3%, and 1.6% of patients, respectively (RR, 0.25; 95% CI, 0.03 to 2.27; $p = 0.18$), while any event was observed in 9.3%, 16.5%, and 11.5% of patients, respectively (RR, 0.52; 95% CI, 0.24 to 1.14; $p = 0.10$). Serious bleeding, defined as a fall in hemoglobin ≥ 2 g or the need for a transfusion, occurred in 1.7%, 1.7%, and 3.3% of patients, respectively. A majority of events were associated with cardiac catheterization.

The remaining trials investigated the potential advantages of combination therapy (UFH plus aspirin) over aspirin monotherapy. Consistent trends across each study favored combined pharmacotherapy and its ability to reduce the combined end point of death or MI.

2.1.1 Therapeutic Levels of Anticoagulation

The optimal level of anticoagulation in patients with ACS is not well defined. The reason likely relates to inherent complexities in the pharmacokinetics and pharmacodynamics of UFH, the dynamic nature of coronary arterial thrombosis, and the use of coagulation tests designed primarily to assess hemostatic potential. The activated partial thromboplastin time (APTT), used widely to monitor UFH, provides a general assessment of coagulation potential; however, it is most sensitive to factor IIa activity.

The “therapeutic” level of anticoagulation with UFH may vary with disease state. In venous thromboembolism, heparin levels > 0.2 U/mL (protamine titration method) accompanied by APTT values > 1.5 times the upper limit of control appear to reduce the recurrence of thromboembolism.^{85,86} A similar APTT range may be sufficient in the context

of left ventricular mural thrombus prophylaxis⁸⁷ and the maintenance of coronary arterial patency following tPA administration.⁸⁸

The TIMI IIIB Investigators⁸⁹ evaluated the relationship between levels of systemic anticoagulation and clinical events among 1,473 patients with NSTEMI ACS. Although heparin levels (chromogenic anti-IIa activity) and APTT values (measured serially over a 72 to 96 h UFH infusion period) did not differ significantly between patients experiencing vs those free of clinical events (spontaneous ischemia, MI, death), a trend favored heparin levels > 0.2 U/mL and APTTs in the 45 to 60 s range as being protective. In addition, high levels of anticoagulation (APTT > 80 s) were not beneficial.

The GUSTO-IIb study⁹⁰ included 5,861 patients with NSTEMI ACS who received UFH for 72 h. A dose of 60 U/kg bolus with a 12 U/kg/h infusion resulted in the highest proportion of APTT values within the prespecified target range of 50 to 70 s. After adjustment for baseline variables, a higher 12-h APTT was associated with an increased risk of death or reinfarction at 30 days. A prolonged APTT at 6 h increased the risk of moderate or severe bleeding. An APTT of 50 to 60 s at 12 h was associated with the lowest risk of hemorrhagic complications.

The available evidence supports a weight-adjusted dosing regimen with UFH as a means to provide a more predictable and constant level of systemic anticoagulation.^{91–93} An initial bolus of 60 to 70 U/kg (maximum 5,000 U) and initial infusion of 12 to 15 U/kg/h (maximum 1,000 U/h) titrated to a target APTT of 50 to 75 s may be optimal.⁵ A “weaning” schedule at the time of treatment completion may reduce rebound thrombin generation and ischemic/thrombotic events,⁹² although proving the clinical benefit of this approach will require an adequately powered randomized clinical trial.

2.2 Low-Molecular-Weight Heparins

Low-molecular-weight heparin (LMWH) preparations represent a class of heparin-derived compounds with varying molecular weights (2,000 to 10,000 d LMWH has pharmacokinetic and pharmacodynamic biophysical advantages over unfractionated heparin (UFH) [see chapter by Hirsh et al in this supplement for details].

2.2.1 Clinical Trials With LMWHs

Petersen et al⁹⁴ conducted a systematic overview of efficacy and bleeding comparing enoxaparin with UFH in the six randomized controlled trials that compared these antithrombin therapies among NSTEMI ACS pa-

tients (Table 4). Using data from the 21,946 randomized patients, they report no significant difference in death at 30 days for enoxaparin vs UFH (3.0% vs 3.0%; OR 1.00; 95% CI, 0.83 to 1.17) and a significant reduction in the 30-day composite of death or MI favoring enoxaparin over UFH (10.1% vs 11.0%; OR 0.91; 95% CI, 0.83 to 0.99). They observed no significant differences in blood transfusion (OR 1.01; 95% CI, 0.89 to 1.14) or major bleeding (OR 1.04; 95% CI, 0.83 to 1.30) at 7 days.

The original experience with LMWH⁹⁵ included 205 patients with unstable angina who were randomized to either aspirin (200 mg/d), aspirin (200 mg/d) plus UFH (5,000-U bolus, 400 U/kg/d infusion), or aspirin (200 mg/d) plus high-dose nadroparin (214 IU/kg BD by subcutaneous [SC] injection). Patients underwent continuous ST-segment monitoring during the first 48 h of treatment. Overall, 73% of patients receiving LMWH were free from ischemic events, compared with 39% of those receiving UFH and 40% of patients given aspirin alone. There were also fewer silent ischemic events in the LMWH group (18%) compared with those receiving UFH (29%) or aspirin alone (34%). Recurrent angina occurred in 9%, 26%, and 19% of patients, respectively, and MIs were not observed in LMWH-treated patients (compared with 1% in the UFH and 6% in the aspirin-alone groups). Major bleeding occurred infrequently in all treatment groups.

A larger study, Fragmin During Instability in Coronary Artery Disease (FRISC)-1,⁹⁶ included 1,506 patients with unstable angina and NSTEMI who were randomized to LMWH (dalteparin, 120 IU/kg SC [maximum 10,000 IU] bid for 6 days, then 7,500 IU qd for 35 to 45 days) or placebo; all patients received aspirin (300 mg first dose, 75 mg/d thereafter). The risk of death or MI was reduced by 63% with LMWH at day 6. The probability of death, MI, and need for revascularization remained lower in the LMWH-treated patients at 40 days; however, results showed little difference between groups beyond the treatment period. Survival analysis revealed a risk of reactivation (recurrent myocardial ischemia) and reinfarction when the dose was reduced (at day 7).

In the FRIC (Fragmin in Unstable Coronary Artery Disease) study,⁹⁷ 1482 patients with NSTEMI ACS were assigned to either twice-daily weight-adjusted SC injections of LMWH (dalteparin 120 IU/kg) or dose-adjusted (target APTT 1.5 times the control) IV UFH for 6 days (acute treatment phase). Patients randomized to UFH received a continuous infusion for at least 48 h and were given the option of either continuing the infusion or changing to an SC regimen (12,500 U q12h). In the blinded comparison that took place from days 6 to 45 (prolonged treatment phase), patients received either LMWH (dalteparin, 7,500 IU SC qd)

or placebo. During the first 6 days, the rate of death, recurrent angina and MI was 7.6% in the UFH-treated patients and 9.3% in the LMWH-treated patients (RR 1.18; 95% CI, 0.84 to 1.66).

The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in NonQ wave Coronary Events) trial⁹⁸ randomly assigned 3,171 patients with angina at rest or NSTEMI to either LMWH (enoxaparin, 1 mg/kg SC bid) or IV UFH (target APTT 55–85 s). Therapy was continued for a minimum of 48 h (maximum 8 days). The median duration of therapy for both groups was 2.6 days. At 14 days, the risk of the composite end point of death, recurrent angina, or MI was 16.6% among patients receiving LMWH and 19.8% for patients given UFH (RR, 16%).

The TIMI 11B study compared enoxaparin and UFH in 3910 patients with NSTEMI ACS.⁹⁹ The trial design had several unique features. First, enoxaparin therapy was initiated with a 30-mg IV bolus, followed by 1 mg/kg SC bid. Second, UFH treatment was given according to a weight-adjusted dosing strategy (70 U/kg bolus, followed by 15 U/kg/h infusion to a target APTT 1.5 to 2.5 times control). Lastly, there was an out-of-hospital treatment phase comparing enoxaparin and placebo for approximately 6 weeks (patients \geq 65 kilograms received $<$ 60 mg SC bid; those $<$ 65 kg received 45 mg SC bid for a total of 43 days). Treatment with enoxaparin was associated with a significant reduction in the composite outcome of death, MI, or urgent revascularization compared with UFH at day 14 (14.2% vs 16.7%; relative RR 15%; $p = 0.03$). The FRAX. I.S. (Fraxiparine in Ischemic Syndromes)¹⁰⁰ study compared the efficacy of nadroparin vs UFH in 3,468 patients with NSTEMI ACS. Patients were randomized to either UFH, 6-day treatment with nadroparin (86 IU/kg IV bolus, 86 IU/kg SC bid) or 14-day treatment with nadroparin. The combined outcome of cardiovascular death, MI, and recurrent/refractory angina at 14 days occurred in 18.1%, 17.8%, and 20% of patients, respectively (no significant difference). Hemorrhagic events were more common in patients receiving nadroparin for 14 days.

The FRISC II (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease)¹⁰¹ included 2,267 patients with unstable coronary disease who received 5 days of dalteparin (120 IU/kg SC q12h) and were then randomized to either an invasive or conservative treatment strategy. In separate randomization, patients received either dalteparin (5,000–7,500 IU SC q12h) or placebo injections for 3 months. By 30 days there was a significant reduction in death or MI favoring dalteparin-treated patients (3.1% vs 5.9%; $p = 0.002$). The benefit diminished over the next 2 months.

In a prospective, comparative study of LMWH preparations,¹⁰² 438 patients with NSTEMI ACS were

Table 4—NSTE ACS Treated With LMWH Compared With UFH or Placebo: Clinical Information and Results (Section 2.2.1)*

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death (%)	RR (95% CI)	MI/Unstable Angina (%) (95% CI)	Composite (%) Death, MI, Recurrent Angina (95% CI)	Ischemia (%) (95% CI)	Major Bleeding (%)† (95% CI)	Comments																																																																																																																	
LMWH vs UFH Antman et al ⁹⁹ / 1999	Acute phase (14 d): ENOX: Enoxaparin 30 mg bolus followed by 1 mg/kg SC bid; UFH: UFH bolus 70 U/kg and initial infusion of 50 U/kg/h for 3–8 d; Chronic phase: ENOX: Enoxaparin 40 mg (< 65 kg) to 60 mg (≥ 65 kg) SC q12h	Acute phase: 3,910; ENOX: 1,953; UFH: 1,957; Chronic phase: ENOX: 1,179; UFH: 1,185	14 d	At 48 h: ENOX: 11/1,953 (0.6%); UFH: 6/1,957 (0.3%); RR: 1.84 (0.68, 4.99); 14 d: ENOX: 43/1,953 (2.2%); UFH: 55/1,957 (2.1%); RR: 0.78 (0.52, 1.17); 43 d: ENOX: 75/1,953 (3.8%); UFH: 78/1,957 (4.0%); RR: 0.96 (0.69, 1.33)	MI only; at 48 h: ENOX: 26/1,953 (1.3%); UFH: 38/1,957 (1.9%); RR: 0.68 (0.41, 1.13); 14 d: ENOX: 83/1,953 (4.2%); UFH: 105/1,957 (5.4%); RR: 0.78 (0.58, 1.05); 43 d: ENOX: 107/1,953 (5.5%); UFH: 129/1,957 (6.6%); RR: 0.82 (0.63, 1.07)	14 d: ENOX: 277/1,953 (14.2%); UFH: 326/1,957 (16.7%); RR: 0.82 (0.69, 0.98); 43 d: ENOX: 337/1,953 (17.3%); UFH: 385/1,957 (19.7%); RR: 0.85 (0.72, 1.00)	NR	At 72 h: ENOX: 16/1,938 (0.8%); UFH: 14/1,936 (0.7%); RR: 1.14 (0.56, 2.33); 14 d: ENOX: 29/1,938 (1.5%); UFH: 19/1,936 (1.0%); RR: 1.52 (0.86, 2.71); 43 d: ENOX: 34/1,179 (2.9%); UFH: 18/1,185 (1.5%); RR: 1.90 (1.08, 3.34)	TIMI 11B trial																																																																																																																		
				ENOX: 23/2,024 (1.1%); UFH: 17/1,957 (0.9%); RR: 1.31 (0.70, 2.44)	ENOX: 73/1,998 (3.6%); UFH: 86/1,938 (4.4%); RR: 0.82 (0.61, 1.12)	ENOX: 255/2,006 (12.7%); UFH: 275/1,937 (14.2%); RR: 0.90 (0.76, 1.05)	ENOX: 81/1,997 (4.1%); UFH: 95/1,937 (4.9%); RR: 0.83 (0.62, 1.10)	ENOX: 59/1,940 (3.0%); UFH: 44/1,965 (2.2%); RR: 1.36 (0.92, 2.0)	A to Z trial																																																																																																																		
				ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	MI only; 48 h: ENOX: 11/1,607 (0.7%); UFH: 14/1,564 (0.9%); RR: 0.70 (0.34, 1.69); 14 d: ENOX: 51/1,607 (3.2%); UFH: 70/1,564 (4.5%); RR: 0.70 (0.48, 1.01); 30 d: ENOX: 62/1,607 (3.9%); UFH: 81/1,564 (5.2%); RR: 0.74 (0.52, 1.03)	48 h ENOX: 99/1607 (6.2%); UFH: 115/1,504 (7.4%); RR: 0.83 (0.62, 1.09); 14 d: ENOX: 266/1,607 (16.6%); UFH: 309/1,564 (19.8%); RR: 0.84 (0.72, 0.97); 30 d: ENOX: 318/1,607 (19.8%); UFH: 364/1,564 (23.3%); RR: 0.85 (0.74, 0.97)	TIA 14 d: ENOX: 1/1,607 (0.1%); UFH: 8/1,564 (0.5%); RR: 0.12 (0.02, 0.97)	ENOX: 102/1,607 (6.5%); UFH: 107/1,564 (7.0%); RR: 0.93 (0.71, 1.21)	ESSENCE study																																																																																																																		
				ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 3,171; ENOX: 1,607; UFH: 1,564	48 h: ENOX: 8/1,607 (0.3%); UFH: 7/1,564 (0.4%); RR: 1.11 (0.4, 3.06); 14 d: ENOX: 36/1,607 (2.2%); UFH: 36/1,564 (2.3%); RR: 0.97 (0.62, 1.54); 30 d: ENOX: 47/1,607 (2.9%); UFH: 57/1,564 (3.6%); RR: 0.80 (0.55, 1.17)	ENOX: 23/2,024 (1.1%); UFH: 17/1,957 (0.9%); RR: 1.31 (0.70, 2.44)	ENOX: 255/2,006 (12.7%); UFH: 275/1,937 (14.2%); RR: 0.90 (0.76, 1.05)	ENOX: 81/1,997 (4.1%); UFH: 95/1,937 (4.9%); RR: 0.83 (0.62, 1.10)	ENOX: 59/1,940 (3.0%); UFH: 44/1,965 (2.2%); RR: 1.36 (0.92, 2.0)	A to Z trial																																																																																																																
				ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,005/2,018 (99.3%)	ENOX: 1,933/1,952 (99.0%); UFH: 2,0

Table 4—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death (%) RR (95% CI)	MI/Unstable Angina (%) (95% CI)	Composite (%) Death, MI, Recurrent Angina (95% CI)	Ischemia (%) (95% CI)	Major Bleeding (%)† (95% CI)	Comments
Cohen et al ¹⁰⁶ /2002	ENOX: Enoxaparin 1 mg/kg SC injection q12h; UFH: 5,000-U IV bolus, maintenance infusion of 1,000 U/h adjusted to an aPTT of 1.5–2.5 times control	525; ENOX: 315; UFH: 210	96 h	ENOX: 8/315 (2.5%); UFH: 4/210 (1.9%); RR: 1.33 (0.41, 4.37)	ENOX: 21/315 (6.7%); UFH: 15/210 (7.1%); RR: 0.93 (0.49, 1.77)		ENOX: 2/315 (0.6%); UFH: 9/210 (4.3%); RR: 0.15 (0.03, 0.68)	ENOX: 1/315 (0.3%); UFH: 2/210 (1.0%); RR: 0.33 (0.03, 3.65)	ACUTE II; all patients received aspirin and tirofiban
FRAXIS Study Group ¹⁰⁰ /1999	Nad6 6-day treatment with nadroparin (86 IU/kg IV bolus, 86 IU/kg SC bid); Nad14: 14-d treatment with nadroparin (86 IU/kg IV bolus, 86 IU/kg SC bid); UFH: UFH IV bolus 5,000 IU followed by infusion of 1,250 IU/h	3,468; Nad6: 1,166; Nad14: 1,151; UFH: 1,151	Acute: 14 d; chronic: 3 mo	At 6 d: Nad6: 15/1,166 (1.3%); Nad14: 11/1,151 (1.0%); UFH: 14/1,151 (1.2%); RR Nad vs UFH: 0.92 (0.48, 1.76); at 14 d: Nad6: 23/1,166 (2.0%); Nad14: 24/1,151 (2.1%); UFH: 19/1,151 (1.7%); RR Nad v UFH: 1.23 (0.72, 2.08); at 3 mo, Nad6: 49/1,166 (4.2%); Nad14: 50/1,151 (4.3%); UFH: 41/1,151 (3.6%); RR Nad v UFH 1.20 (0.84, 1.71)	At 6 d: Nad6: 32/1,166 (2.8%); at 14 d: 27/1,151 (2.3%); UFH: 29/1,151 (2.5%); RR Nad vs UFH: 1.01 (0.65, 1.57); at 14 days: Nad6: 52/1,166 (4.5%); Nad14: 41/1,151 (3.6%); UFH: 42/1,151 (3.7%); RR Nad vs UFH: 1.10 (0.77, 1.57); at 3 mo, Nad6: 71/1,166 (6.1%); Nad14: 72/1,151 (6.2%); UFH: 64/1,151 (5.6%); RR Nad v UFH 1.11 (0.83, 1.48)	Nad14: 207/1,166 (17.8%); Nad14: 230/1,151 (20.0%); UFH: 207/1,151 (18.1%); RR Nad vs UFH: 1.05 (0.90, 1.22)	NR	At 6 d Nad6: 8/1,166 (0.7%); Nad14: 15/1,151 (1.3%); UFH: 11/1,151 (1.0%); RR Nad vs UFH: 2.62 (1.33, 5.16); at 14 d Nad6: 17/1,166 (1.5%); Nad14: 40/1,151 (3.5%); UFH: 18/1,151 (1.6%); RR Nad vs UFH: 1.57 (0.93, 2.66); between day 1 and month 3 intracranial hemorrhage; Nad6: 1 (0%); Nad14: 2 (0.1%); UFH: 4 (0.3%)	FRAXIS; numbers estimated from % presented in chapter
Goodman et al ¹⁰⁵ /2003; Fitchett et al/2006	ENOX: Enoxaparin 1 mg/kg SC bid for 48 h; UFH: 70 U/kg IV bolus followed by a 15 U/kg/h continuous infusion, titrated aPTT of 1.5 to 2 times for 48 h; All patients: aspirin and eptifibatide	n = 746; ENOX: 380; UFH: 366; n = 639; ENOX: 325; UFH: 314	96 h; 30 d; 2.5 yr	30 d: ENOX: 9/380 (2.4%); UFH: 15/366 (4.1%); RR: 0.58 (0.26, 1.3); 2.5 yr: ENOX: 23/380 (6.1%); UFH: 39/366 (10.7%); RR: 0.57 (0.35, 0.93)	30 d: ENOX: 15/380 (4.0%); UFH: 21/366 (5.8%); RR: 0.69 (0.36, 1.31); 2.5 yr: ENOX: 33/380 (8.7%); UFH: 45/366 (12.3%); RR: 0.71 (0.46, 1.08)	30 d: ENOX: 53/380 (14.0%); UFH: 59/366 (16.1%); RR: 0.87 (0.61, 1.22); 2.5 yr: ENOX: 90/380 (23.7%); UFH: 107/366 (29.5%); RR: 0.80 (0.63, 1.02)	ENOX: 20/380 (5.3%); UFH: 32/366 (8.7%); RR: 0.60 (0.35, 1.03)	INTERACT	

Table 4—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death (%)	RR (95% CI)	MI/Unstable Angina (%) (95% CI)	Composite (%) Death, MI, Recurrent Angina (95% CI)		Ischemia (%) (95% CI)	Major Bleeding (%)† (95% CI)	Comments
Klein et al ^{97/1997}	Acute phase: Dalteparin 120 anti-Xa U/kg SC bid; UFH dose-adjusted IV; Chronic phase Dalteparin 7,500 anti-Xa SC qd	Acute Phase n = 1,482: Dalteparin: 751; Placebo: 731; Chronic phase n = 1,133: Dalteparin: 567; Placebo: 565	Acute phase, 6 d; Chronic phase, 6 to 45 d	Acute phase: Dalteparin: 11/751 (1.5%); UFH: 3/731 (0.4%)	RR: 3.37 (1.01, 11.24); Chronic phase: Dalteparin: 11/562 (2.0%); UFH: 11/561 (2.0%)	Acute phase: Dalteparin: 19/751 (2.6%); UFH: 23/731 (3.2%)	RR: 0.81 (0.45, 1.48); Chronic phase: Dalteparin: 17/562 (3.1%); UFH: 20/561 (3.6%)	Acute phase: Dalteparin: 69/751 (9.3%); UFH: 55/731 (7.6%)	NR	Acute phase: Dalteparin: 8/751 (1.1%); UFH: 7/731 (1.0%)	FRIC
	ENOX: 9.97%; ENOX: 4.493; UFH: 4.985	30 d	ENOX: 160/4,983 (3.2%); UFH: 155/4,985 (3.1%)	RR: 0.89 (0.40, 2.02)	ENOX: 585/4,993 (11.7%); UFH: 633/4,985 (12.7%)	ENOX: 729/4,993 (14.6%); UFH: 753/4,985 (15.1%); RR: 0.97 (0.88, 1.06)	ENOX: 454/4,993 (9.1%); UFH: 379/4,985 (7.6%)	1.20 (1.05, 1.36)	SYNERGY		
	ENOX: 141; ENOX: weight-adjusted 100 antifactor Xa U/kg SC bid; Dalteparin: weight-adjusted 120 antifactor Xa U/kg SC bid up to 10,000 U/injection; UFH: initial bolus 70 U/kg, then continuous IV infusion	30 d	ENOX: 0/46; Dalteparin: 0/48; UFH: 5/47 (10.6%)	ENOX vs UFH: 0.09 (0.01, 1.63); RR dalteparin vs UFH: 0.09 (0.01, 1.57)	ENOX: 6/46 (13.0%); Dalteparin: 9/48 (18.8%); UFH: 13/47 (27.7%); RR ENOX vs dalteparin: 0.70 (0.27, 1.80); RR ENOX vs UFH: 0.47 (0.20, 1.13); RR dalteparin vs UFH: 0.68 (0.32, 1.43); RR LMWH vs UFH: 0.58 (0.30, 1.11)	ENOX: 0/46; Dalteparin: 1/48 (2.1%); UFH: 0/47	ENOX vs Dalteparin: 0.35 (0.01, 8.32) RR Dalteparin vs UFH: 2.98 (0.12, 70.37); RR LMWH vs UFH: 1.50 (0.06, 36.14)	ARMADA			

Table 4—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death (%) RR (95% CI)	MI/Unstable Angina (%) (95% CI)	Composite (%) MI, Recurrent Angina (95% CI)	Ischemia (%) (95% CI)	Major Bleeding (%)† (95% CI)	Comments
FRISC II Investigators ¹⁰¹ / 1999	Dalteparin group 120 IU/kg SC bid for 1-5 days (open treatment phase)	2,105; LMWH:1,049 Placebo: 1,056	Treatment phase: 90 d	At 3 mo: Dalteparin: 14/1,049 (1.3%) Placebo: 17/1,056 (1.6%) RR: 0.83 (0.41, 1.67)	Total treatment period: Death, MI, both At 3 mo: Dalteparin: 70/1,049 (6.7%) Placebo: 85/1,056 (8.0%) RR: 0.81 (0.60, 1.10)	At 3 mo: Dalteparin: 328/1,129 (29.1%) Placebo: 374/1,121 (33.4%) RR: 0.87 (0.77, 0.99)		At 3 mo: Dalteparin: 34/1,049 (3.3%) Placebo: 16/1,056 (1.5%) RR: 2.14 (1.19, 3.85)	FRISC II trial
FRISC II Investigators ¹⁰⁵ / 1999a	Dalteparin vs placebo 7,500 IU SC bid for 5-90 d	2,457 Invasive: 1,207 Noninvasive: 1,226	Invasive vs noninvasive phase:180 d	At 6 mo: Invasive: 36/1,207 (2.9%) Noninvasive: 36/1,226 (1.9%) RR: 1.02 (0.64, 1.60)	Total treatment period: Death, MI, both At 6 mo: Invasive: 113/1,207 (9.4%) Noninvasive: 148/1,226 (12.1%) RR: 0.78 (0.62, 0.98)	At 6 mo: Dalteparin: 428/1,129 (38.4%) Placebo: 440/1,121 (39.9%) RR: 0.96 (0.87, 1.07)		Dalteparin: Invasive: 13/606 (2.3%) Non-invasive: 21/617 (3.6%) RR: 0.63 (0.32, 1.25) Placebo: Invasive: 7/601 (1.3%) Noninvasive: 11/609 (1.9%) RR: 0.64 (0.25, 1.65)	

Table 4—Continued

Study/yr	Interventions	Patients Analyzed, No.	Length of Follow-up	Death (%) RR (95% CI)	MI/Unstable Angina (%) (95% CI)	Composite (%) Death, MI, Recurrent Angina (95% CI)	Ischemia (%) (95% CI)	Major Bleeding (%)† (95% CI)	Comments
Roe ¹⁶³ /2003	Early treatment Late treatment Crossover design: 12- 24 h of double-blind therapy, then crossover to a second bolus of blinded study drug followed by an open-label eptifibatide infusion. Eptifibatide bolus dose of 100 µg/kg then infusion of 2.0 µg/kg/min Placebo bolus dose of 100 µg/kg then infusion of 2.0 µg/kg/min	311	72 h or until the time of hospital discharge	Early: 2/153 (1.3%) Late: 0/158	Early: 3/153 (2.0%) Late: 2/158 (1.3%)	Early: 8/153 (5.2%) Late: 7/158 (4.4%)	Early: 4/153 (2.6%) Late: 5/158 (3.2%)	Overall, major bleeding: Early: 12/153 (7.9%) Late: 8/158 (5.1%) Non-CABG major bleeding: Early: 7/153 (4.6%) Late: 5/158 (3.2%)	Early All patients received aspirin (162- 325 mg) and SC UFH

*Nad6 = nadroparin at 6 days; Nad14 = nadroparin at 14 days. See Table 3 for expansion of abbreviations. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

†Major bleeding: overt bleeding resulting either in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop ≥ 3 g/dL, or the requirement of transfusion of ≥ 2 U blood (TIMI criteria).

randomized to receive either subcutaneous injections of 100 mg enoxaparin bid or 175 IU/kg tinzaparin qd for 7 days. There were no differences in the primary outcome (death, MI, refractory angina, or recurrence of unstable angina); however, there was a lower incidence of recurrent unstable angina and need for revascularization at 30 days among enoxaparin-treated patients ($p = 0.02$). Hemorrhagic events were similar in the two groups.

The A to Z Trial¹⁰³ assessed the efficacy and safety of the combination of enoxaparin and tirofiban compared with UFH and tirofiban among NSTEMI ACS patients. Among the enoxaparin patients, 8.4% ($n = 169$) experienced the composite of death, MI or refractory ischemia at 7 days compared with 9.4% ($n = 184$) who were randomized to UFH (HR, 0.88; 95% CI, 0.71 to 1.08). Superiority of enoxaparin over UFH was not achieved but the results met the prespecified definition of noninferiority. Combined TIMI bleeding (major or minor) was low and not different between the groups (3.0% vs 2.2%, $p = 0.13$).

In order to better determine the role of enoxaparin in an invasive management strategy, the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and GP IIb/IIIa Inhibitors) Investigators¹⁰⁴ randomized 10,027 high-risk NSTEMI ACS patients intended for an early invasive strategy to receive enoxaparin or UFH. At 30 days, the primary composite end point of death or MI was 14.0% among enoxaparin patients and 14.5% among those randomized to UFH (OR, 0.96; 95% CI, 0.86 to 1.06). These results satisfied the predefined criteria for noninferiority. Importantly, among the subgroup of patients undergoing PCI, there were no differences in ischemic events (including abrupt closure) between the treatment groups. Major bleeding was significantly increased with enoxaparin compared with UFH when measured according to the TIMI scale but not with the GUSTO scale.

2.2.2 Duration of Treatment With LMWHs

The potential benefit of extended therapy with LMWH has been evaluated in several clinical trials. In the FRISC study,⁹⁷ dalteparin was continued at a dose of 7,500 IU IV qd for 39 days. A minority of patients experienced NSTEMI; no additional benefit from extended therapy was observed. Similar findings were reported with enoxaparin (40 or 60 mg bid for 43 days) in the TIMI 11B trial.⁹⁹

The FRISC I trial⁹⁶ suggested that extended LMWH treatment (dalteparin 7,500 IU qd) might benefit selected patients. The combined end point of death or MI was reduced by 40% ($p = 0.003$) at day

40 in nonsmokers, as well as in patients with NSTEMI, diabetes mellitus, prior MI, age > 70 years, and those treated for heart failure. During extended therapy patients with an initial troponin level > 0.1 $\mu\text{g/L}$ derived the greatest overall benefit (RR, 0.48 at day 40; $p = 0.01$).⁹⁶

In the extended follow-up phase of TIMI 11B, continued treatment beyond the initial hospital phase did not provide added benefit (17.3 vs 19.7%; relative RR, 12%; $p = 0.05$).⁹⁹

The FRISC II trial^{101,105} extended several important observations made in FRISC I. Patients experiencing chest pain associated with either ECG changes or elevated cardiac biomarkers received dalteparin 120 IU/kg SC q12h plus aspirin. Those assigned to a noninvasive strategy received dalteparin for 5 to 7 days (until an exercise tolerance test was performed). Patients in the invasive strategy arm of the trial received dalteparin for at least 5 days (until an invasive procedure was performed). Thereafter, either dalteparin (5,000 IU SC bid [women < 80 kg, men < 70 kg] or 7,500 IU SC bid in heavier patients) or placebo was given by self-injection for 90 days.

A total of 2,267 patients were included in the noninvasive arm of FRISC II.^{101,105} At 90 days there was a nonsignificant 19% RR reduction in death or MI associated with prolonged dalteparin administration (RR, 0.81; 95% CI, 0.60 to 1.10; $p = 0.17$). The combined end point was 3.1% in dalteparin-treated patients compared with 5.9% in those given placebo at 30 days (RR, 0.53; 95% CI, 0.35 to 0.80; $p = 0.002$). The triple composite of death, MI, or revascularization was 13% lower ($p = 0.031$) at 90 days with prolonged LMWH administration. The rates of hemorrhage were 2.2% and 1.2%, respectively.

2.2.3 Platelet GP IIb/IIIa Inhibitors and LMWH: Combination Therapy

The contribution of platelets and coagulation proteins to coronary arterial thrombosis provides a biological rationale for combination pharmacotherapy in patients with NSTEMI ACS. In the Antithrombotic therapy Combination Using Tirofiban and Enoxaparin II (ACUTE II) study,¹⁰⁶ 525 patients with NSTEMI ACS were treated with tirofiban plus aspirin and randomized to receive either UFH (5,000-U bolus, 1,000 U/h adjusted to an APTT of 1.5 to 2.5 times control), or enoxaparin (1.0 mg/kg SC q12h). Therapy was administered for 24 to 96 h. In-hospital death or MI occurred in 9.0% and 9.2% of patients, respectively; however, refractory ischemia requiring urgent revascularization and rehospitalization because of unstable angina occurred more frequently in the UFH group (4.3% vs 0.6%; RR, 0.72;

$p = 0.01$; and 7.1% vs 1.6%; RR, 0.44; $p = 0.002$, respectively). TIMI major bleeding occurred in 1.0% and 0.3% of patients, respectively.

In a GUSTO IV substudy,¹⁰⁷ 646 patients received dalteparin (120 IU/kg SC bid), aspirin and either 24 or 48 h of abciximab given as an initial bolus followed by a continuous infusion. Patients receiving the LMWH plus the GP IIb/IIIa inhibitor were compared with the larger number of nonstudy patients who received UFH and the GP IIb/IIIa inhibitor. Death or MI at 30 days occurred in 9.6% of dalteparin-treated patients and 8.5% of UFH-treated patients. The rates of major non-CABG bleeding were 1.2% and 0.7%, respectively.

The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary syndrome Treatment (INTERACT) study¹⁰⁸ randomized 746 patients with NSTEMI ACS to open-label enoxaparin (1 mg/kg SC bid) or UFH (70 U/kg bolus, 15 U/kg/h to a target APTT of 1.5 to 2.0 times control) for 48 h. All patients received aspirin and eptifibatide (180 µg/kg bolus, 2 µg/kg/min infusion). Major non-CABG bleeding at 96 h (primary safety outcome) was significantly lower among enoxaparin-treated patients than those receiving UFH (1.8% vs 4.6%, $p = 0.03$). Minor bleeding occurred more often in the enoxaparin group (30.3% vs 20.8%, $p = 0.003$). Patients receiving enoxaparin were less likely to experience ischemia (determined by continuous ECG monitoring) [primary outcome] during the initial (14.3% vs 25.4%, $p = 0.002$) and subsequent (12.7% vs 25.9%, $p < 0.0001$) 48-h monitoring periods. Combined death or MI at 30 days was also lower in enoxaparin-treated patients (5% vs 9%, $p = 0.03$).

2.2.4 Anticoagulation Monitoring With LMWHs

LMWH preparations catalyze thrombin inhibition to a lesser extent than UFH and, as a result, they induce less prolongation of the APTT. Because prolongation of the APTT correlates inversely with the anti-Xa:anti-IIa ratio, tinzaparin (ratio 1.5:1) produces a higher APTT (for an equivalent dose) than enoxaparin (ratio 3.0:1). The more rapid dissipation of anti-IIa activity following LMWH administration also contributes to a weaker effect of LMWH preparations on the APTT.

Anti-Xa activity can be measured by chromogenic and chrometric assays. As with other coagulation tests, variability does exist. A majority of clinical trials, whether based on deep vein thrombosis prophylaxis, venous thromboembolism treatment, or ACS, have not required drug titration according to anti-Xa monitoring; however, an ability to define safe and effective levels of anticoagulation is important

for clinical reasons. Defining a target level of factor Xa inhibition is also important in patients with altered drug clearance such as renal insufficiency (particularly with LMWH preparations characterized by a high anti-Xa:anti-IIa ratio). Lastly, monitoring capabilities may be useful when drug reversal is required because of the possibility of hemorrhagic complications during invasive procedures with inherent bleeding risks.

In the TIMI 11A study,¹⁰⁹ there was a relationship between enoxaparin dose and hemorrhagic complications, particularly in those undergoing coronary angiography, PCI, or CABG. Patients receiving enoxaparin at a dose of 1.25 mg/kg q12h had a peak anti-Xa activity (chromogenic assay) of 1.5 IU/mL, while those given 1.0 mg/kg q12h averaged 1.0 IU/mL. Anti-Xa activity among patients with major hemorrhage was 1.8 to 2.0 IU/mL. An analysis of anti-Xa inhibition pharmacokinetics revealed that high trough and peak activity (upper quintiles) was associated with major hemorrhagic events.¹⁰⁹

The optimal level of factor Xa inhibition has not been determined for patients with ACS receiving LMWH. The available information derived from nonrandomized clinical studies of PCI suggests that anti-Xa activity > 0.5 IU/mL is associated with a low incidence of ischemic/thrombotic and hemorrhagic events.^{110,111} Global coagulation tests, including traditional APTT and activated clotting time (ACT) assays, may provide some insight for LMWH preparations characterized by low anti-Xa:anti-IIa activity.¹¹²

2.2.5 Antithrombin Therapies and Renal Function

The mechanism of LMWH clearance is predominantly renal (nonsaturable), which explains the linear characteristics of reported elimination curves.^{113,114} Renal performance may not influence pharmacokinetics following single-dose IV administration of enoxaparin.^{111,115}

The anti-Xa pharmacokinetics of several other LMWH preparations have been investigated in small-scale, multiple-dose trials. The findings suggest that severe renal insufficiency (creatinine clearance < 30 mL/min) is associated with reduced drug clearance, particularly with lower molecular-weight (or proportion of short chain molecules) preparations.

Alexander et al⁸⁰ have reported in the large CRUSADE observational registry that 13.8% of NSTEMI ACS patients treated with a LMWH receive an excess dose based on body weight only. After considering other baseline characteristics, those receiving an excessive dose of LMWH had an increased risk of major bleeding compared with those not receiving excess dosing (OR, 1.39; 95% CI, 1.11 to 1.74).

2.2.6 LMWH and PCI

Increasingly, LMWH is used in place of UFH for treatment of patients with NSTEMI/ACS, many of whom undergo PCI.^{111–122} Because of difficulties monitoring levels of anticoagulation with LMWH during PCI, empiric dosing algorithms have been developed.¹²³ Enoxaparin is the most commonly used LMWH in this setting. Thus, if the last dose of enoxaparin was given < 8 h before PCI, no additional enoxaparin is used. When the last dose of enoxaparin was given 8 to 12 h before PCI, a 0.3 mg/kg bolus of IV enoxaparin is advocated at the time of PCI, whereas if the last enoxaparin dose was administered > 12 h before PCI, conventional anticoagulation therapy is recommended. This strategy was used successfully in the large SYNERGY Trial.¹⁰⁴

In small pilot studies, enoxaparin appears to be safe when used in combination with tirofiban¹⁰⁶ or eptifibatide¹²⁴ during PCI. Favorable outcomes have also been reported using a combination of dalteparin and abciximab in patients undergoing PCI.¹²⁵

Montalescot et al have reported the results of the Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) trial.¹²⁶ In this open-label RCT, 3,528 patients scheduled for PCI were randomized to receive one of two doses of IV enoxaparin (0.5 or 0.75 mg/kg) or UFH (adjusted using ACT). Approximately 40% of the patients also received GP IIb/IIIa inhibitors. The primary end point was the 48 h occurrence of major or minor bleeding (not related to CABG surgery). There was a significant reduction in the primary end point with the lower dose enoxaparin compared with UFH but not with the higher dose (5.9% vs 8.5%, $p = 0.01$; 6.5% vs 8.5%, $p = 0.051$). In a multivariate model examining the risk factors for non-CABG associated bleeding, female sex, age > 75 and use of GP IIb/IIIa inhibitors were all associated with an increased risk of bleeding. The trial was insufficiently powered to draw definitive conclusions regarding the ischemic events. The incidence of the 30-day composite of all-cause death, nonfatal MI, or urgent target vessel revascularization was 6.2% with the lower enoxaparin dose, 6.8% with the higher dose and 5.8% with UFH (p values for comparisons against UFH were 0.51 and 0.30, respectively).

Short-term administration of LMWH after PCI does not significantly reduce the occurrence of early ischemic events. In the Antiplatelet Therapy alone vs. Lovenox plus Antiplatelet therapy in patients at increased risk of Stent Thrombosis (ATLAST) trial,²⁸ 1102 patients at increased risk of stent thrombosis (ST-elevation MI within 48 h, diffuse distal disease, large thrombus volume, acute closure, or residual dissection) were randomly assigned to receive either

enoxaparin (40 or 60 mg given SC q12h for 14 days) or placebo; all patients received aspirin (325 mg/d) and ticlopidine (250 mg bid) for 14 days.²⁸ The primary end point, a 30-day composite of death, nonfatal MI, and urgent revascularization, occurred in 1.8% of patients given enoxaparin and in 2.7% of those given placebo ($p = 0.295$). LMWH treatment has no effect on restenosis.^{127–129}

2.2.7 Economic Implications of LMWH vs UFH in ACSs

The interesting paradox of UFH is that this biological product has proven clinical benefit in ACS despite the significant difficulties that are often encountered in establishing and maintaining a stable level of anticoagulation with it. These difficulties have suggested that anticoagulants with simpler dosing and more reliable therapeutic effects might offer significant clinical advantages over UFH in the treatment of acute coronary syndrome patients. Further, such advantages might justify the higher prices associated with new drugs.

Of the LMWHs developed to supplant UFH, enoxaparin has been studied in the largest number of ACS patients and is the most widely used alternative to UFH in North America. A recent metaanalysis⁹⁴ of six trials comparing these two agents in almost 22,000 patients found an overall 9% relative reduction in death or MI at 30 days for enoxaparin with no effect on overall mortality and no difference in major bleeding at 7 days. The first of these six trials, ESSENCE,¹³⁰ also had an economic analysis from the US societal perspective. In this analysis, a mean of 2.5 days of enoxaparin therapy cost \$155 vs \$80 for UFH. Enoxaparin was associated with a reduction at 30 days in the rates of diagnostic catheterization and PCI and a trend toward reduced length of stay in the ICU. These resource trends resulted in a cost offset for enoxaparin of over \$700 by hospital discharge, making enoxaparin therapy clinically superior and also less expensive from a societal perspective and a hospital perspective. The US-discounted average wholesale price for enoxaparin in 2006 is higher than it was when this study was performed and the contemporary price of the enoxaparin regimen for the United States would be around \$250, but this increase does not alter the major conclusions of the study.

The most recent of the six randomized trials of enoxaparin vs UFH, SYNERGY, found no differences in death or MI out to 30 days and no effects on coronary revascularization rates but a modest increase in major bleeding.¹⁰⁴ While the cause of the loss of enoxaparin's clinical advantage seen in the earlier trials remains speculative, from an economic

point of view, one change is particularly noteworthy. In the ESSENCE Trial,⁹⁸ which enrolled patients between 1994 and 1996, only about 50% of patients overall underwent diagnostic angiography during the index hospitalization. In contrast, in SYNERGY the diagnostic catheterization rate was 92%.¹⁰⁴ Since the economic benefits seen in ESSENCE were related primarily to the effects of enoxaparin on the use of invasive procedures, it may be that the use of such procedures in virtually all patients in SYNERGY precluded the opportunity to observe a similar economic benefit.

In view of these differences among studies and in the absence of a definitive way to resolve them, it is reasonable to consider the economics in terms of the clinical context in which therapy is to be used. If the practice environment is more like that in ESSENCE,⁹⁸ with approximately half of the patients not referred for early invasive management, it is reasonable to expect some cost offsets with enoxaparin from reduced complications and related procedures, as was seen in the ESSENCE economic substudy.¹³⁰ If the practice pattern is more like that in SYNERGY, with almost all patients undergoing in-hospital coronary angiography, no offsets on the incremental cost of the enoxaparin regimen are likely and the value-for-money case is less clear.

2.3 Selective Factor Xa Inhibitors: Synthetic Pentasaccharide

The pentasaccharide sequence contained within heparin molecules is a prerequisite for antithrombin binding and subsequent coagulation protease neutralization. Fondaparinux (molecular weight, 1,728 d) is a synthetic pentasaccharide that facilitates antithrombin (indirect)-mediated factor Xa (selective) inhibition. It does not inactivate thrombin. The anti-Xa activity of the drug increases with increasing plasma concentrations, peaking within 3 h of SC administration. Elimination occurs solely through renal mechanisms and the plasma half-life is 17 to 21 h.

Fondaparinux is currently Food and Drug Administration-approved for prophylaxis of DVT in patients undergoing hip fracture, hip replacement, or knee replacement surgery. It has been extensively studied among patients with NSTEMI/ACS. In the Pentasaccharide in Unstable Angina (PENTUA) study,¹³¹ 1,138 patients were randomized to receive either enoxaparin (1 mg/kg SC bid) or fondaparinux (2.5 mg, 4 mg, 8 mg, or 12 mg SD daily) for 3 to 7 days. The primary efficacy end point was a composite of death, MI, or recurrent ischemia at 9 and 30 days. The composite end point was reached in 40.2%, 30.0%, 43.5%, 41.0%, and 34.8%, of patients respec-

tively, and major and minor bleeding at day 30 occurred in 4.8%, 3.9%, 5.0%, 5.8%, and 4.7% of patients, respectively.

The Arixtra Study in PCI: a Randomized Evaluation (ASPIRE) Trial¹³² randomized 350 patients undergoing elective or urgent PCI to receive UFH or one of two doses of IV fondaparinux (2.5 or 5.0 mg). The primary safety outcome was the occurrence of major and minor bleeding. Mehta et al¹³² reported a bleeding incidence of 7.7% in the UFH group compared with 6.4% in the combined fondaparinux groups ($p = 0.06$; HR, 0.81; 95% CI, 0.35 to 1.84). There was less bleeding noted with the lower dose of fondaparinux compared with the higher dose (3.4% vs 9.6%, $p = 0.06$). There was no difference among the groups with regard to the ischemic composite of death, MI, urgent revascularization or GP IIb/IIIa inhibitor bail-out. There was noted a numerical excess of in-laboratory thrombotic events (abrupt closure or angiographic thrombus) among the fondaparinux groups compared with the UFH group (nine cases in 2.5-mg fondaparinux group, five cases in the 5.0-mg group, and two cases in the UFH group).

Yusuf et al reported on the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial,¹³³ a randomized, blinded, double-dummy trial comparing a mean of 6 days of fondaparinux (2.5 mg/d SQ) with enoxaparin (1 mg/kg bid, adjusted to once daily for patients with a creatinine clearance < 30 mL/min) among 20,078 patients with NSTEMI/ACS. During PCI, there was an algorithm to supplement anticoagulation in both study arms with additional UFH being used in the enoxaparin group and additional IV fondaparinux and UFH ("as per local standard" in the fondaparinux group). The primary outcome measure was the 9-day composite of death, MI, or refractory ischemia. There were a similar number of ischemic events occurring between the groups (5.8% fondaparinux vs 5.7% enoxaparin; HR, 1.01; 95% CI, 0.90 to 1.13). This satisfied the trial's prespecified noninferiority criteria. There was less major bleeding observed with fondaparinux compared with enoxaparin (2.2% vs 4.1%; HR, 0.52; 95% CI, 0.44 to 0.61; $p < 0.001$). At 180 days, there were fewer deaths (5.8% vs 6.5%; HR, 0.89; 95% CI, 0.80 to 1.00) and a reduction in the death or MI composite (10.5% vs 11.4%; HR, 0.92; 95% CI, 0.84 to 1.00) associated with fondaparinux use. There was an increased risk of coronary guide-catheter thrombus formation with fondaparinux compared with enoxaparin (0.9% vs 0.4%, $p = 0.001$) though rates of death or MI were similar between the groups in this population. A strategy of providing additional UFH boluses as per the local

standard (eg, 50 to 60 U/kg UFH) during PCI might decrease the risk of catheter thrombosis.

2.4 Direct Thrombin Inhibitors

2.4.1 Hirudins

Direct thrombin inhibitors were developed to overcome several limitations of heparin compounds, which include platelet-activating properties, complex pharmacokinetics (with UFH) and an inability of the heparin-antithrombin complex to inactivate fibrin-bound thrombin. Hirudin is a potent, direct, bivalent thrombin inhibitor. The terminal half-life is 60 min with clearance by renal mechanisms.

Hirudin doses used in clinical practice prolong APTT and ACT coagulation tests and correlate fairly well with plasma concentrations. In contrast, the thrombin time is too sensitive for application in dose titration and assessment of anticoagulant effects, while the PT is not sensitive enough.

2.4.2 Clinical Trial Results

A systematic overview using individual patient data of randomized clinical trials was performed to obtain precise estimates of direct thrombin inhibitors in the management of ACS (STE and NSTEMI ACS; PCI).¹³⁴ A total of 11 randomized trials including 35,970 patients were identified and included in the analysis. Compared with UFH, direct thrombin inhibitors were associated with a lower risk of death or MI at the end of treatment (up to 7 days) [4.3% vs 5.1%; OR, 0.85; 95% CI, 0.77 to 0.94; $p = 0.001$] and at 30 days (7.4% vs 8.2%; OR, 0.91; 95% CI, 0.84 to 0.99; $p = 0.02$). Seven trials included 30,154 patients with either NSTEMI ACS or undergoing PCI (Fig 2). In patients with NSTEMI ACS, treatment with a direct thrombin inhibitor was associated with a reduction in death or MI compared with UFH (3.7% vs 4.6%; OR, 0.80; 95% CI, 0.70 to 0.92). Similar reductions were observed in PCI trials (3.0% vs 3.8%; OR, 0.79;

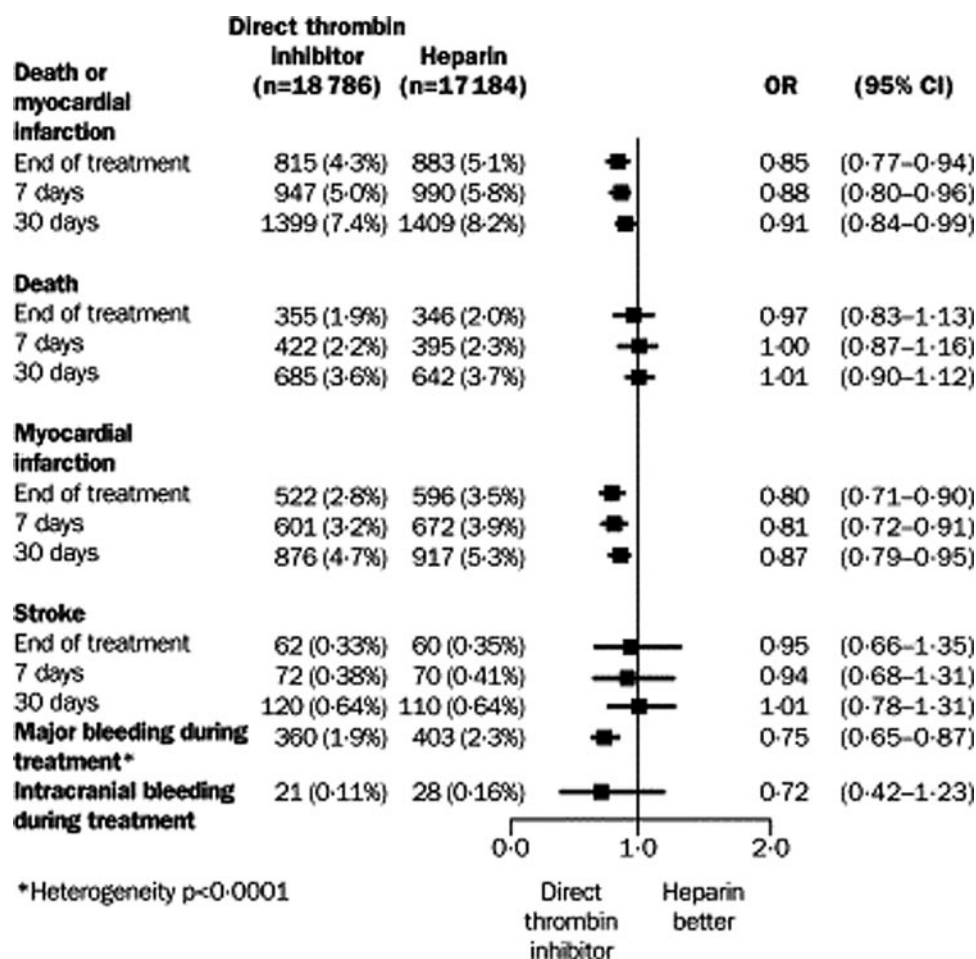


FIGURE 2. Systematic overview of DTI trials among patients with ACS and who are undergoing PCI. This shows a comparison of DTIs with heparin on both the ischemic and safety end points. Reprinted with permission from Elsevier (*The Lancet* 2002; 359:294–302).

95% CI, 0.59 to 1.06). There was a statistically insignificant increased rate of major bleeding with direct thrombin inhibitors in trials of ACS (1.6% vs 1.4%; OR, 1.11; 95% CI, 0.93 to 1.34), but there was a significant decrease in PCI trials (3.7% vs 7.6%; OR, 0.46; 95% CI, 0.36 to 0.59). There were no differences in the rates of intracranial hemorrhage.

The risk reduction in death or MI at the end of treatment was similar in trials comparing hirudin or bivalirudin with UFH, but there was a slight excess with univalent inhibitors (4.7% vs 3.5%; OR, 1.35; 95% CI, 0.89 to 2.05). When major bleeding outcomes were analyzed by agent, hirudin was associated with an excess of major bleeding compared with UFH (1.7% vs 1.3%; OR, 1.28; 95% CI, 1.06 to 1.55), whereas both bivalirudin (4.2% vs 9.0%; OR, 0.55, 95% CI, 0.34 to 0.56) and the univalent inhibitors (such as argatroban) (0.7% vs 1.3%; OR, 0.55; 95% CI, 0.25 to 1.20) were associated with lower rates of major bleeding.

2.4.3 Individual Trials

In the GUSTO-IIb trial,³ patients with NSTEMI ACS were randomized to receive either UFH or desirudin (0.1 mg/kg IV bolus, 0.1 mg/kg/h infusion). At 24 h, the risk of death or nonfatal MI was reduced in hirudin-treated patients (1.3% vs 2.1%; $p = 0.001$). The primary end point of death or nonfatal MI at 30 days was reached in 8.9% and 9.8% of patients, respectively (OR, 0.89; 95% CI, 0.79 to 1.00; $p = 0.06$). The risk of moderate bleeding was increased with hirudin treatment (8.8% vs 7.7%; $p = 0.03$).

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study¹³⁵ randomized 909 patients with unstable angina or suspected MI without ST-segment elevation to receive UFH (5,000-U bolus, 1,000 to 1,200 U/h infusion), low-dose hirudin (0.2 mg/kg bolus, 0.1 mg/kg/h infusion) or moderate-dose hirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion). Doses of UFH and hirudin were titrated to a target APTT of 60 to 100 s. Compared with UFH, hirudin reduced the composite incidence of cardiovascular death, MI, or refractory angina at 7 days (OR, 0.57; 95% CI, 0.32 to 1.02) and a composite of death, MI, or refractory/severe angina requiring revascularization at 7 days (OR, 0.49; 95% CI, 0.27 to 0.86). Overall event rates were lowest in the moderate-dose hirudin group. Major hemorrhage occurred in approximately 1% of patients and did not differ significantly among the groups. The incidence of minor bleeding was higher in hirudin-treated patients (21.3%, 16.2%, and 1.5% for moderate-dose hirudin, low-dose hirudin, and UFH, respectively).

The favorable results in OASIS prompted a large

phase III trial, OASIS-2,¹³⁶ which randomized 10,141 patients with NSTEMI ACS to a 72-h infusion of either moderate-dose hirudin (as defined in OASIS-1) or UFH. The primary outcome (composite of death or MI at 7 and 35 days) was reported in 3.6% and 4.2% of patients (OR, 0.87; 95% CI, 0.75 to 1.01), respectively.

Hirudin is almost exclusively excreted through the kidneys and, as a result, renal function must be considered carefully prior to administration. The majority of clinical trials excluded patients with a creatinine level ≥ 2.0 mg/dL. Even in the setting of mild renal impairment (CrCl, 50 to 80 mL/min), excessive levels of systemic anticoagulation (and accompanying risk for hemorrhage) can occur with nonmodified dosing. When hirudins are administered to patients with renal insufficiency, frequent APTT monitoring is highly recommended.

2.4.4 Bivalirudin

Bivalirudin is a 20-amino acid polypeptide that interacts with both the active and anion binding sites of thrombin; however, once bound there is a slow but progressive recovery of the active site function of thrombin, which may play a role in preserving hemostatic potential.

Bivalirudin has been studied extensively in variety of acute care settings, including NSTEMI ACS and PCI; it is FDA-approved for use in patients undergoing PCI including those with a recent NSTEMI ACS. Approval was based on data from several randomized clinical trials,¹³⁷ the largest performed by Bittl et al.¹³⁸ Among 4,312 patients with new-onset, severe, accelerating, or rest angina undergoing PCI, a 22% reduction in death, MI, or urgent revascularization at 7 days was observed in those given bivalirudin compared with UFH (6.2% vs 7.9%; $p = 0.03$). The absolute and relative differences were maintained at 90 days. There was a marked RR reduction (62%) in bleeding complications among bivalirudin-treated patients compared with those treated with UFH.

In the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-1) pilot trial,¹³⁹ 1,056 patients scheduled for elective or urgent PCI were randomized to receive weight-dosed and ACT-guided UFH or bivalirudin (0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion during the procedure). GP IIb/IIIa inhibitors were given at the investigator's discretion and 72% received during PCI. The primary efficacy measure was the 48-h composite of death, MI, or repeat revascularization, the incidence of which did not differ between the groups (5.6% bivalirudin vs 6.9% UFH, $p = 0.40$). Bleeding was also similar between the groups (2.1% vs 2.7%, $p = 0.52$).

The follow-up study to REPLACE was the REPLACE-2 trial,¹⁴⁰ a randomized, double-blind comparison of bivalirudin with provisional GP IIb/IIIa inhibitors vs UFH with planned use of GP IIb/IIIa inhibitors. Dosing of bivalirudin was as employed in REPLACE, while the UFH dose was decreased to 65 U/kg bolus followed by ACT-guided adjustments (done in a blinded fashion). The coprimary end points were the 30-day quadruple composite of death, MI, urgent revascularization, and major bleeding, and the 30-day ischemic triple end point of death, MI, or urgent revascularization. The bivalirudin strategy was noninferior to the UFH-based strategy with regard both to the quadruple composite and the 30-day ischemic outcomes (9.2% vs 10.0%; OR, 0.92; 95% CI, 0.77 to 1.09 for the quadruple end point; 7.6% vs 7.1%; OR, 1.09; 95% CI, 0.90 to 1.32 for the triple end point). Bivalirudin was associated with less major bleeding than UFH (2.4% vs 4.1%; $p \leq 0.001$).

Bivalirudin has also been studied extensively in the setting of NSTEMI ACS as “upstream” anticoagulant therapy. The TIMI 8 Investigators planned a large (5,320 patients) randomized clinical trial¹⁴¹ comparing bivalirudin (0.1 mg/kg bolus followed by a 0.25 mg/kg/h infusion) with UFH (70 U/kg bolus followed by a 15 U/kg/h infusion) among patients with NSTEMI ACS. The trial was terminated by the sponsor because of a change in the development plans after only 133 patients had been randomized into the trial. The 14-day composite of death or MI occurred in 9.2% of UFH patients compared with 2.9% bivalirudin patients (OR, 0.30; 95% CI, 0.06 to 1.53). Major bleeding was reported in three UFH patients and in no patients receiving bivalirudin.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)¹⁴² trial was a large, open-label randomized trial comparing three antithrombotic strategies in patients presenting with a NSTEMI ACS who were scheduled to be treated with an early invasive strategy. The investigators randomized 13,819 patients to receive UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor or bivalirudin alone. There were three primary end points assessed at 30 days: a composite of death, MI, or unplanned revascularization; major bleeding not related to CABG surgery; and a composite of these ischemic and bleeding end points. The investigators prespecified both noninferiority as well as superiority tests. Bivalirudin plus a GP IIb/IIIa inhibitor was noninferior to heparin plus a GP IIb/IIIa inhibitor with regard to the ischemic composite (7.7% vs 7.3%), the bleeding composite (5.3% vs 5.7%) and the combined composite (11.8% vs 11.7%). Bivalirudin alone compared with heparin plus a GP IIb/IIIa inhibitor was noninferior on the ischemic end point (7.8% vs 7.3%) and superior on the bleeding end point (3.0% vs 5.7%;

RR, 0.53; 95% CI, 0.43 to 0.65) and on the combined composite (10.1% vs 11.7%; RR, 0.86; 95% CI, 0.77 to 0.97).

Several notable features of this trial deserve comment to place the results in context when considering these antithrombotic strategies for “upstream” use. First, as would be expected in a trial promoting the early invasive management strategy, times from randomization to cardiac catheterization were very rapid (a median of approximately 4 h in all treatment groups). Second, the bivalirudin alone strategy seemed to require concomitant thienopyridine administration to maintain noninferiority on the ischemic composite with the heparin plus GP IIb/IIIa inhibitor.

2.4.5 Argatroban

Argatroban is a small molecule, peptidomimetic arginine derivative that interacts solely with the active site of thrombin (competitive, univalent inhibitor). It is metabolized in the liver, a process that generates several active intermediates. Although the half-life of argatroban is not altered by renal function, clearance is markedly influenced by hepatic performance. Argatroban, like the other IV univalent direct thrombin antagonists, inogatran and efegatran, has not undergone definitive clinical trial evaluation for use among patients with NSTEMI ACS.

2.5 Heparin-Induced Thrombocytopenia

For recommendations about prevention and management of heparin-induced thrombocytopenia, please see chapter by Warkentin et al in this supplement.

Recommendations for Anticoagulant Therapies

1. For all patients presenting with NSTEMI ACS, we recommend anticoagulation with UFH or LMWH or bivalirudin or fondaparinux over no anticoagulation (Grade 1A).

a. We recommend weight-based dosing of UFH and maintenance of the APTT Between 50 and 70 s (Grade 1B).

b. We recommend against routine monitoring of the anticoagulant effect of LMWH (Grade 1C). Careful attention is needed to appropriately adjust LMWH dose in patients with renal insufficiency.

2. For NSTEMI ACS patients who will undergo an early invasive strategy of management (ie, diagnostic catheterization followed by anatomy-driven revascularization):

a. We recommend UFH (with a GP IIb/IIIa inhibitor) over either LMWH or fondaparinux (Grade 1B).

b. We suggest bivalirudin over UFH in combination with a thienopyridine as an

initial antithrombotic strategy in patients with moderate- to high-risk features presenting with a NSTEMI/ACS and scheduled for very early coronary angiography (< 6 h) [Grade 2B].

3. For NSTEMI/ACS patients in whom an early conservative or a delayed invasive strategy of management is to be used:

a. We recommend fondaparinux over enoxaparin (Grade 1A). For patients treated with upstream fondaparinux and undergoing PCI, we recommend that additional IV boluses of UFH be given at the time of the procedure (for example, 50 to 60 U/kg) as well as additional IV doses of fondaparinux (2.5 mg if also receiving a GP IIb/IIIa inhibitor and 5 mg if not) [Grade 1B]. Additionally, PCI operators should regularly flush the catheters with UFH during the procedure as well.

b. We recommend LMWH over UFH (Grade 1B). We recommend continuing LMWH during PCI treatment of patients with NSTEMI/ACS when LMWH has been started as the upstream anticoagulant (Grade 1B). If the last dose of enoxaparin was given \leq 8 h prior to PCI, we recommend no additional anticoagulant therapy (Grade 1B). If the last dose of enoxaparin was given 8 to 12 h before PCI, we recommend a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (Grade 1B).

4. In low- to moderate-risk patients with NSTEMI/ACS undergoing PCI, we recommend either bivalirudin with provisional (bail-out) GP IIb/IIIa inhibitors or UFH plus a GP IIb/IIIa inhibitor over alternative antithrombotic regimens (Grade 1B).

ACKNOWLEDGMENT: The authors would like to thank David Matchar, MD, for his contributions in resource allocation issues.

CONFLICT OF INTEREST DISCLOSURES

Dr. Harrington discloses that he holds a fiduciary position as Director of the Duke Clinical Research Institute (DCRI). Either he or the DCRI have received grant monies from the following: Abbott Laboratories; Abbott Vascular Business; Acorn Cardiovascular; Actelion, Ltd; Acusphere, Inc; Adolor Corporation; Advanced Cardiovascular Systems, Inc; Air Products; PLC; Ajinomoto; Alexion, Inc; Allergan, Inc; Alsus Corporation; Amgen, Inc; Amylin Pharmaceuticals; Anadys; Angel Medical Systems, Inc; AnGes MG Inc; Angiometrx, Inc; ArgiNox Pharmaceuticals; Ark Therapeutics; Astellas Pharma US; Astra Hassle; AstraZeneca; Atritech; Aventis; BARRX Medical, Inc; Baxter; Bayer AG; Bayer Corporation US; Berlex, Inc; Bioheart; Biolex Therapeutics; Biosense Webster, Inc; Biosite, Inc (also Biosite Diagnostics); Biosynexus; Boehringer Ingelheim; Boston MedTech Advisors; Bristol Scientific Corporation; Bristol-Myers Squibb; CanAm Bioresearch; Cardio Thoracic Systems; CardioDynamics International; CardioKinetix; CardioOptics; Celgene Corporation; Celsion Corporation; Centocor; Cerexa, Inc; Chase Medical;

Chugai Pharmaceutical; Cierra Inc; Coley Pharmaceutical Group; Conor Medsystems; Coraetus Genetics; Cordis; Critical Therapeutics; Cubist Pharmaceuticals; CV Therapeutics; Cytokinetics; Daiichi Sankyo; deCode Genetics; Dyax; Echoscans, Inc; Eclipse Surgical Technologies; Edwards Lifesciences; Eli Lilly & Company; EnteroMedics; Enzon Pharmaceutical; EOS Electro Optical Systems; EPI-Q, Inc; ev3, Inc; Evalve, Inc; Flow Cardia Inc; Fox Hollow Pharmaceuticals; Fujisawa; Genentech; General Electric Company; General Electric Healthcare; General Electric Medical Systems; Genzyme Corporation; Getz Bros & Co, Inc; GlaxoSmithKline; Globelimmune; Gloucester Pharmaceuticals; Guidant Pharmaceuticals; HeartScape Technologies; Hoffmann-LaRoche; Human Genome Sciences, Inc; ICAGEN; iCo Therapeutics; IDB Medical; Idenix Pharmaceutical; Indigo Pharmaceutical; INFORMD, Inc; InfraReDx; Inhibitex; Innocoll Pharmaceuticals; Inspire Pharmaceuticals; Intarcia Therapeutics; Integrated Therapeutics Group; Inverness Medical Innovations; Ischemix, Inc; Johnson & Johnson; Jomed, Inc; KAI Pharmaceuticals; Kerberos Proximal Solutions, Inc; Kinetic Concepts, Inc; King Pharmaceuticals; Kuhera Chemical Co; Lilly; Lumen Biomedical, Inc; Medical Educations Solutions Group; Medtronic International; MiniMed; Medi-Flex, Inc; MedImmune; Medtronic AVE; Medtronic Diabetes; Medtronic, Inc; Medtronic Vascular; Merck Group; Microphage, Inc; Millennium Pharmaceutical; Mosby; Mycosol, Inc; NABI Biopharma; Neuron Pharmaceuticals; NicOx; NitroMed; NovaCardia Inc; Novartis AG Group; Novartis Pharmaceuticals; OLG Research; Ortho Biotech; OSI Eyetech; Osiris Therapeutics; Otsuka Pharmaceutical; Pathway Medical Technologies; PDL bio Pharma; PDXRx, Inc; Peregrine Pharmaceuticals; Pfizer; Pharmacocyclics; Pharmaceutics; Pharmassest; Pharsight, Inc; Portola Pharmaceutical; Proctor & Gamble; Radiant; Reata Pharmaceuticals; Recom Managed Systems, Inc; Regado Biosciences; Reliant Pharmaceuticals; Roche Diagnostic Corp; Salix Pharmaceuticals; Sanofi Pasteur, Inc (formerly Aventis-Pasteur); Sanofi-Aventis; Sanofi-Synthelabo; Schering-Plough Corporation; SciClone Pharmaceuticals; Scios; Seredigm; Sichel Technologies; Siemens; Skyline Ventures; Social Scientific Solutions; Spectranetics; Summit; Suneis; TAP Pharmaceutical Products; Tengion; Terumo Corporation; The Medicines Company; Theravance; TherOx, Inc; Thoratec Corporation; Titan Pharmaceuticals; United Therapeutics; Uptake Medical Corporation; Valleylab; Valeant Pharmaceuticals International; Valentis, Inc; Vascular Solutions, Inc; Velocimen, Inc; Veridex; Vertex Pharmaceuticals; VIASYS Healthcare; Vicuron Pharmaceuticals (formerly Versicor); ViroChem Pharma, Inc; Watson Pharmaceuticals; WebMD; Wyeth; Xsira Pharmaceuticals (formerly Norak Biosciences); and/or XTL Biopharma.

Dr. Becker reveals no real or potential conflicts of interest or commitment.

Dr. Cannon discloses that he has received grant monies from Accumetrics, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Sanofi-Aventis, and Schering Plough.

Dr. Lincoff discloses that he has received grant monies from The Medicines Company, Sanofi, Lilly, Pfizer, Schering, and AstraZeneca. He is also on advisory committees for Sanofi, The Medicines Company, and Pfizer.

Dr. Steg discloses that he has received grant monies from Sanofi-Aventis, and consultant fees from Sanofi-Aventis, AstraZeneca, BMS, Boehringer Ingelheim, Takeda, Amgen, Thermedicine, MSD, GSK, and Servier. He has served on the speakers bureau at Sanofi-Aventis, AstraZeneca, BMS, Boehringer Ingelheim, Takeda, Amgen, Thermedicine, MSD, GlaxoSmithKline, and Servier.

Dr. Popma discloses that he has received monies from Cordis, Boston Scientific, Medtronic, and Abbott. He is involved with the

speakers bureaus of Pfizer, BMS, Lilly, and Sanofi, and has served on advisory committees of Medtronic, BSC, Abbott, and Cordis.

Dr. Goodman discloses that he has received grant monies from Biovail, Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-La Roche, Lilly, Merck, Sanofi-Aventis, Schering, and The Medicines Company. He has also received consultant fees from Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-La Roche, Lilly, Sanofi-Aventis, and The Medicines Company.

Dr. Guyatt reveals no real or potential conflicts of interest or commitment.

Dr. Gutterman discloses that he has received grant monies from the Veterans Administration and the National Institutes of Health. He is also a shareholder of Johnson & Johnson and has a relative who is a vice president at Glaxo-Wellcome.

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Chest 2008;133; 670S-707S

DOI 10.1378/chest.08-0691

This information is current as of October 5, 2009

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