Evolution of Antithrombotic Therapy Used in Acute Coronary Syndromes

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Learning Objectives

1. Design an evidence-based treatment plan for a patient with ST-segment elevation myocardial infarction (STEMI).
2. Design an evidence-based treatment plan for a patient with non–ST-segment elevation (NSTE) acute coronary syndrome (ACS).
3. Justify the selection and timing of administration of a 75-mg, 300-mg, 600-mg, or 900-mg initial clopidogrel dose for a patient undergoing percutaneous coronary intervention (PCI) for NSTE ACS or STEMI or receiving fibrinolysis for STEMI.
4. Distinguish the efficacy and safety of prasugrel and clopidogrel for patients undergoing PCI.
5. Analyze the evidence for using rivaroxaban, apixaban, cangrelor, and ticagrelor in place of traditional antithrombotics for treating ACS.
6. Given a patient case, design a plan for improvement in quality care performance.
7. Given a patient case, estimate the patient's risk of major bleeding and recommend therapies to reduce the patient's bleeding risk.

Introduction

Cardiovascular (CV) diseases are the leading cause of hospitalization in the United States, resulting in about 6.2 million hospital discharges per year. Each year, there are more than 1.3 million myocardial infarctions (MIs), and one in five deaths is secondary to coronary heart disease. According to data from the National Registry of Myocardial Infarction, in-hospital mortality has decreased by more than 20% during the past 20 years. Improvements in care that may have contributed to this mortality reduction include greater use of guideline-recommended drugs (e.g., aspirin, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, statins, clopidogrel); reductions in the median door-to-needle time of 30 minutes and corresponding door-to-balloon time of 32 minutes (2006 times of 29 minutes and 79 minutes, respectively); and increased use of percutaneous coronary intervention (PCI).

The proportion of patients with MI presenting with ST-segment elevation (STE) MI compared with non–ST-segment elevation (NSTE) MI decreased from 85.8% in 1990 to 40.9% in 2006. This may be secondary to the use of the more sensitive biomarker troponin; greater use of antecedent revascularization procedures; decreased reinfarction from enhanced medical therapy after an initial event; or prevention of progression of unstable angina to MI through more effective anticoagulant and antiplatelet therapy.

Timeline for Antiplatelet Development

Antiplatelet therapy for patients with either NSTE acute coronary syndrome (ACS) or STEMI has evolved to include more potent inhibitors, such as prasugrel, and in clinical trials, cangrelor, and/or ticagrelor that are used

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. A suggested resource for background information on this topic includes:

- Spinler SA, de Denus S. Acute coronary syndromes. In: Chisholm-Burns M, Wells BG, Schwinghammer TL, Malone PM, Kolesar JM, Rotschafer JC, et al, eds. Pharmacotherapy Principles and Practice. New York: McGraw-Hill, 2010. (In Press).
- Spinler SA, de Denus S. Acute coronary syndromes. In: DiPiro JT, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy, 7th ed. New York: McGraw-Hill, 2008: 249–78.

Abbreviations in This Chapter

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AHA	American Heart Association
CABG	Coronary artery bypass graft
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV	Cardiovascular
CYP	Cytochrome P450
GP	Glycoprotein
LMWH	Low-molecular-weight heparin
MACE	Major adverse cardiac events
MI	Myocardial infarction
NACE	Net adverse clinical events
NNH	Number needed to harm
NNT	Number needed to treat
NSTE	Non–ST-segment elevation
OASIS	Organization to Assess Strategies in Acute Ischemic Syndromes
PCI	Percutaneous coronary intervention
PLATO	PLATelet Inhibition and Patient Outcomes
STE	ST-segment elevation
TIMI	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin

in combination with aspirin and produce faster and more complete platelet aggregation inhibition in a larger percentage of patients than clopidogrel. As use of these newer agents increases, use of the GP IIb/IIIa receptor inhibitors is likely to continue to decline.

Timeline for Anticoagulant Development

Anticoagulants have changed in the past 15 years as well, first with the development of low-molecular-weight heparins (LMWHs), which offer the advantage of consistent anticoagulant effect when administered subcutaneously and dosed by body weight. Later innovations include fondaparinux and bivalirudin, which provide a lower risk of major bleeding. Acutely, we have decreased the duration of therapeutic anticoagulant administration as the percentage of patients undergoing early coronary angiography and PCI has increased. Emerging oral anticoagulants being studied in phase III trials include rivaroxaban and apixaban.

General Overview of ACS Therapy

The American Heart Association (AHA) and American College of Cardiology (ACC) updated their NSTE ACS guidelines in 2007 and STEMI and PCI guidelines in 2007 and 2009, respectively.

Risk Stratification

Patient examination for ACS begins with stratification for risk of death and reinfarction (Figure 1-1). Patients with STEMI are at highest risk of death and reinfarction. A common tool used to assess risk in patients with NSTE ACS is the Thrombolysis in Myocardial Infarction (TIMI) Risk Score (Table 1-1). Features other than an elevated TIMI Risk Score that indicate higher risk include the presence of a positive or elevated troponin concentration (indicating NSTE MI), signs or symptoms of acute heart failure or shock, PCI within the past 6 months, history of coronary artery bypass graft (CABG) surgery, and recurrent angina or ischemic electrocardiographic changes despite initial pharmacologic therapy.

Guideline Recommendations for Antiplatelet and Anticoagulants

Initial treatments of STEMI are outlined in Figure 1-2. The 2007 and 2009 ACC/AHA guideline updates provided new recommendations, including the option of bivalirudin for patients undergoing primary PCI and enoxaparin for patients undergoing secondary PCI after fibrinolytic therapy (Table 1-2). Initial treatments in NSTE ACS are described in Figure 1-3. The 2007 ACC/AHA guidelines for NSTE ACS include a recommendation for early coronary angiography (early invasive) and revascularization with either PCI or CABG surgery in patients with higher risk features or higher TIMI risk score. In 2009, the ACC/AHA PCI update suggested that early intervention in such high-risk patients occur within 12 hours (class IIa recommendation)

In an early invasive strategy in NSTE ACS, the patient is taken to the cardiac catheterization laboratory and undergoes coronary angiography. Based on findings, the patient undergoes immediate PCI or urgent or emergency CABG, or the patient has no revascularization procedure and receives medical management only (Figure 1-3). Specific anticoagulants are recommended based on this risk classification and on initial physician stratification of the patient to receive either the early invasive or early conservative approach. Bivalirudin and fondaparinux are newer anticoagulant options in NSTE ACS. Bivalirudin use in NSTE ACS is limited to patients in the early invasive treatment strategy; fondaparinux as the sole anticoagulant is limited to use in patients in the early conservative treatment strategy whereby angiography is selected for continuing or recurrent ischemia only (Figure 1-3). Other guideline recommendations and levels of evidence are listed in Table 1-2. This chapter is an update on the role of emerging antiplatelets and anticoagulants in ACS.

Newer Antiplatelet Therapies for ACS

Clopidogrel Loading Dose

As described in Table 1-2, different clopidogrel loading doses are recommended depending on whether the patient

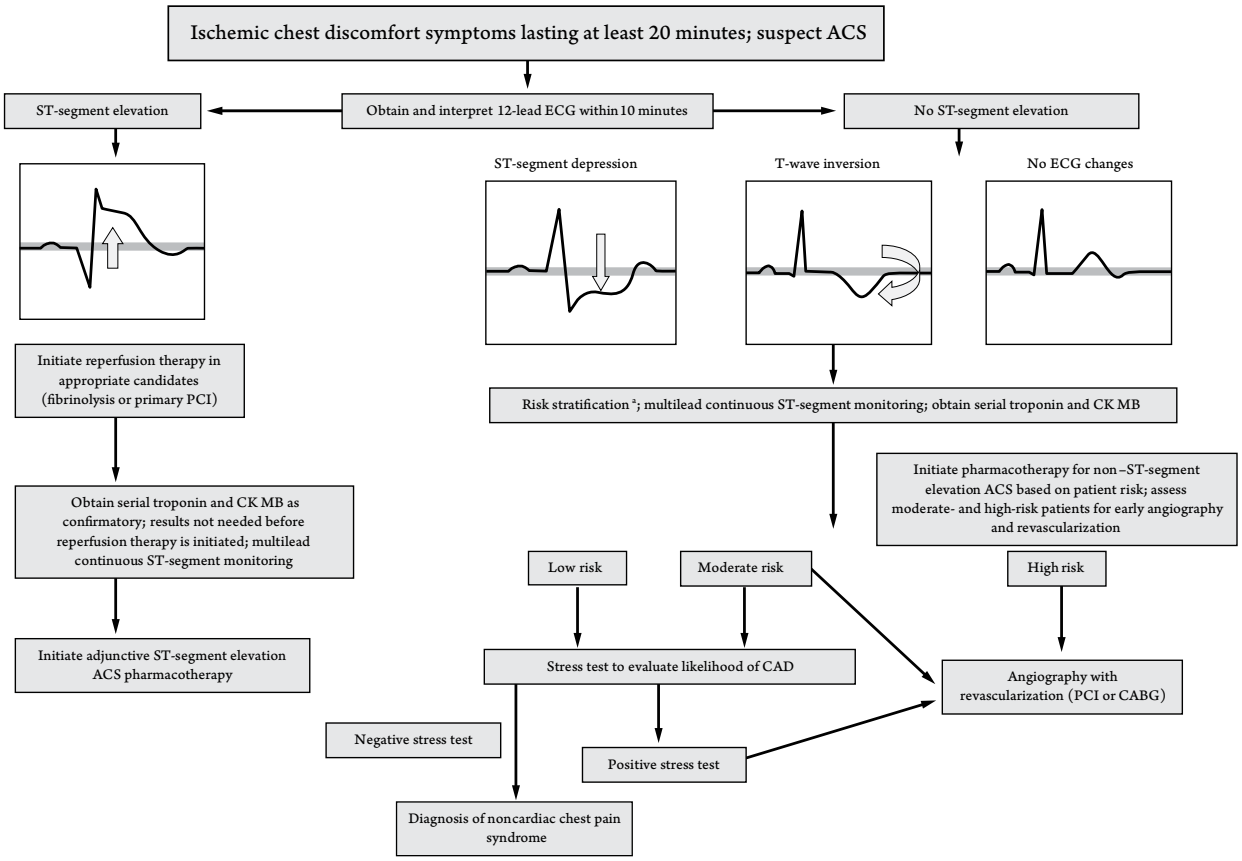

Figure 1-1. Evaluation of the patient with ACS.

[a]As described in Table 1-1.
[b]Positive = above the MI decision limit.
[c]Negative = below the MI decision limit.
ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CK = creatine kinase; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Reproduced with permission from Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, Chessman KH, Hume AL, Hutchison LC, et al, eds. Pharmacotherapy Self-Assessment Program, 6th ed. Book 1: Cardiology. Kansas City: American College of Clinical Pharmacy, 2007:59–83.

is undergoing early PCI, is undergoing conservative therapy for NSTE ACS, or is elderly and receiving fibrinolytics for STEMI. In the 2009 ACC/AHA PCI guidelines, a 300-mg to 600-mg dose of clopidogrel, administered as early as possible before PCI, was recommended. The 2007 ACC/AHA NSTE ACS guidelines recommend a 300-mg clopidogrel loading dose for patients presenting with NSTE ACS and receiving the early conservative approach. For patients presenting with STEMI, the 2007 ACC/AHA guideline update recommends an initial clopidogrel loading dose of 300 mg in patients younger than 75 who are treated with fibrinolytics and no loading dose for older patients treated with fibrinolytics. In patients undergoing PCI after receiving a fibrin-specific fibrinolytic (e.g., alteplase, reteplase, tenecteplase) who did not receive prior thienopyridine therapy, the 2009 ACC/AHA STEMI guideline update recommends a 300-mg clopidogrel loading dose for patients undergoing PCI within 24 hours and a 300-mg to 600-mg loading dose if undergoing PCI after 24 hours. In patients undergoing PCI after receiving streptokinase who did not receive prior thienopyridine therapy, the update recommends a 300-mg loading dose if undergoing PCI within 48 hours and a 300-mg to 600-mg dose if undergoing PCI after 48 hours.

Patients with ACS present with higher baseline platelet aggregation and lower clopidogrel responsiveness than patients with stable coronary artery disease. Therefore, higher doses of clopidogrel produce a more pronounced antiplatelet effect. Controversy exists regarding the comparative antiplatelet effects of higher doses (e.g., 900 mg, 1200 mg) compared with lower doses (e.g., 600 mg) because

Table 1-1. TIMI Risk Score for Risk Stratification in Non–ST-segment Elevation Acute Coronary Syndrome

Medical History	Clinical Presentation
Age 65 years or older	ST-segment depression (0.5 mm or greater)
Three or more risk factors for CAD: • Hypercholesterolemia • Hypertension • Diabetes mellitus • Smoking • Family history of premature CHD	Two or more episodes of chest discomfort within the past 24 hours Positive biochemical marker for infarction (e.g., troponin I or T)
Known CAD (50% or greater stenosis of a coronary artery)	
Use of aspirin within the past 7 days	

Using the TIMI Risk Score

One point is assigned for each of the four medical history and three clinical presentation findings. The total points are calculated, and the patient is assigned a risk for the composite end point of death, myocardial infarction, or urgent need for revascularization within the next 14 days[a]:

High risk score	Medium risk score	Low risk score
5–7 points	3–4 points	0–2 points

[a]0–1 = 4.7%, 2 = 8.3%, 3 = 13.2%, 4 = 19.9%, 5 = 26.2%, 6–7 = 40.9%

CAD = coronary artery disease; CHD = coronary heart disease; TIMI = Thrombolysis in Myocardial Infarction.

some studies suggest greater platelet inhibition, whereas others do not.

Because clopidogrel is a prodrug that undergoes metabolism in a two-step process mediated by cytochrome P450 (CYP) -1A2, -2B6, -3A4, -2C9, and -2C19, administration before PCI results in faster onset and peak effect than administration at the time of PCI. In a study of healthy volunteers, hourly measurement of the degree of platelet inhibition showed that doses of 600 mg and 900 mg produced platelet inhibition of about 70% to 80% within the first 2 hours after administration, whereas a dose of 300 mg achieved only about 50% platelet inhibition within the first 7 hours after administration.

Another study of patients with NSTE ACS undergoing PCI reported a lower percentage who did not achieve ADP platelet aggregation inhibition of at least 70% at 16–20 hours after initial clopidogrel loading doses of 600 mg versus 300 mg; a significant reduction in the rate of CV death at 1 month was seen in the 600-mg clopidogrel group. However, loading doses of 300 mg have proved beneficial in larger clinical trials. A 300-mg loading dose followed by 75 mg once daily was studied in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial in patients with NSTE ACS. This trial established the benefit of the 300-mg loading dose because a reduction in the rate of death, MI, or stroke was evident within the first 24 hours versus placebo. In addition, the benefit of clopidogrel in patients undergoing PCI was apparent within the first 15 hours after administration of the 300-mg loading dose compared with initial doses of 75 mg daily without a loading dose.

The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs-Optimal Antiplatelet Strategy for InterventionS (CURRENT OASIS)-7 trial was a 2 × 2 factorial trial in 25,087 patients with either NSTE ACS or STEMI and planned early angiography and PCI. Researchers compared the frequency of CV death, MI, or stroke at 30 days between high loading dose and high maintenance dose clopidogrel (i.e., 600-mg loading dose with 150 mg daily on days 2–7 and 75 mg daily on days 8–30) with usual clopidogrel dosing (i.e., 300-mg loading dose plus 75 mg daily), as well as a second randomization comparing aspirin 300–325 mg to aspirin 75–81 mg daily. Overall, no significant difference was seen in CV death, MI, or stroke, nor was a significant difference seen in major bleeding between aspirin doses or between double-dose versus standard-dose clopidogrel. However, stent thrombosis was lower in the double-dose clopidogrel group than in the standard-dose clopidogrel group. In the subgroup of 17,232 patients who did undergo PCI, there was a significant reduction in CV death, MI, or stroke, as well as in MI and stent thrombosis in patients receiving double-dose clopidogrel. A significant interaction occurred with aspirin dose, and patients receiving higher-dose aspirin had the lowest rate of stent thrombosis. Another continuing trial, LOAD & GO, is assessing loading doses of 300 mg, 600 mg, and 900 mg in patients undergoing primary PCI for STEMI.

The timing of clopidogrel loading doses in ACS is also of concern. For patients undergoing primary PCI for STEMI, clopidogrel 300–600 mg should be administered as soon as possible, preferably in the emergency department. In

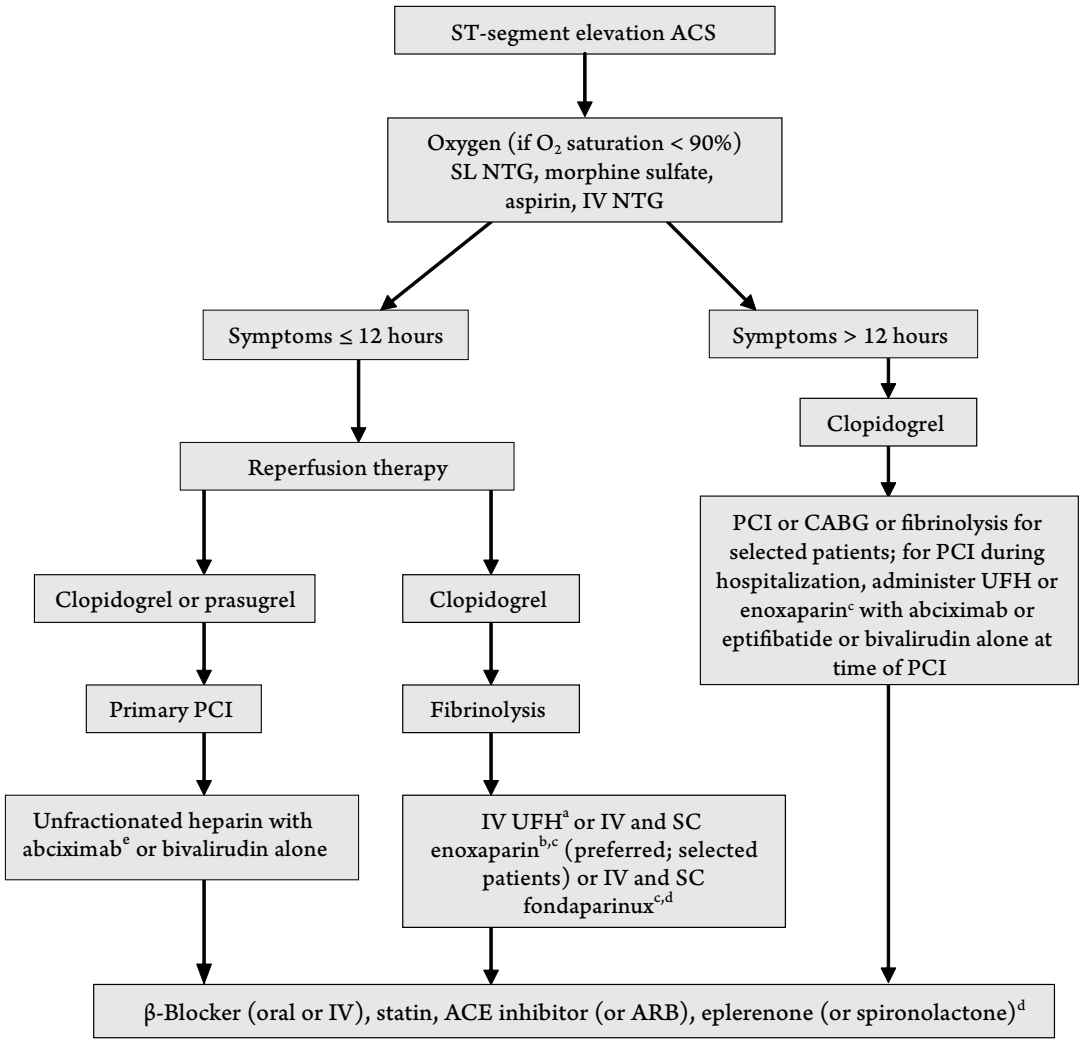

Figure 1-2. Initial pharmacotherapy for ST-segment elevation myocardial infarction.

[a]For at least 48 hours.
[b]See Table 1-2 for dosing and specific types of patients who should not receive enoxaparin.
[c]For the duration of hospitalization, up to 8 days.
[d]For selected patients; see Table 1-2.
[e]Alternatively, eptifibatide or tirofiban.
ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; IV = intravenous; NTG = nitroglycerin; PCI = percutaneous coronary intervention; SL = sublingual; UFH = unfractionated heparin.

primary PCI, few patients are likely to require CABG surgery. For example, the incidence of CABG was 1.7% in the recent Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial of patients with STEMI. During hospitalization for NSTE ACS, however, more patients require CABG surgery than do those with STEMI, making practitioners somewhat reluctant to administer a thienopyridine that might require discontinuation to avoid bleeding in patients undergoing CABG surgery. For example, in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry of patients with NSTE ACS, 12% of patients required CABG surgery during hospital admission. Therefore, in patients undergoing CABG surgery, the 2009 ACC/AHA STEMI and PCI update recommends that clopidogrel be withheld for at least 5 days when CABG is planned and can be delayed. Therefore, in centers with a larger percentage of patients requiring CABG surgery, clinicians may be more reluctant to initiate clopidogrel until the patient's coronary anatomy is known and the need for CABG surgery has been excluded.

The timing of clopidogrel administration has been investigated in the small Antiplatelet Therapy for Reduction in

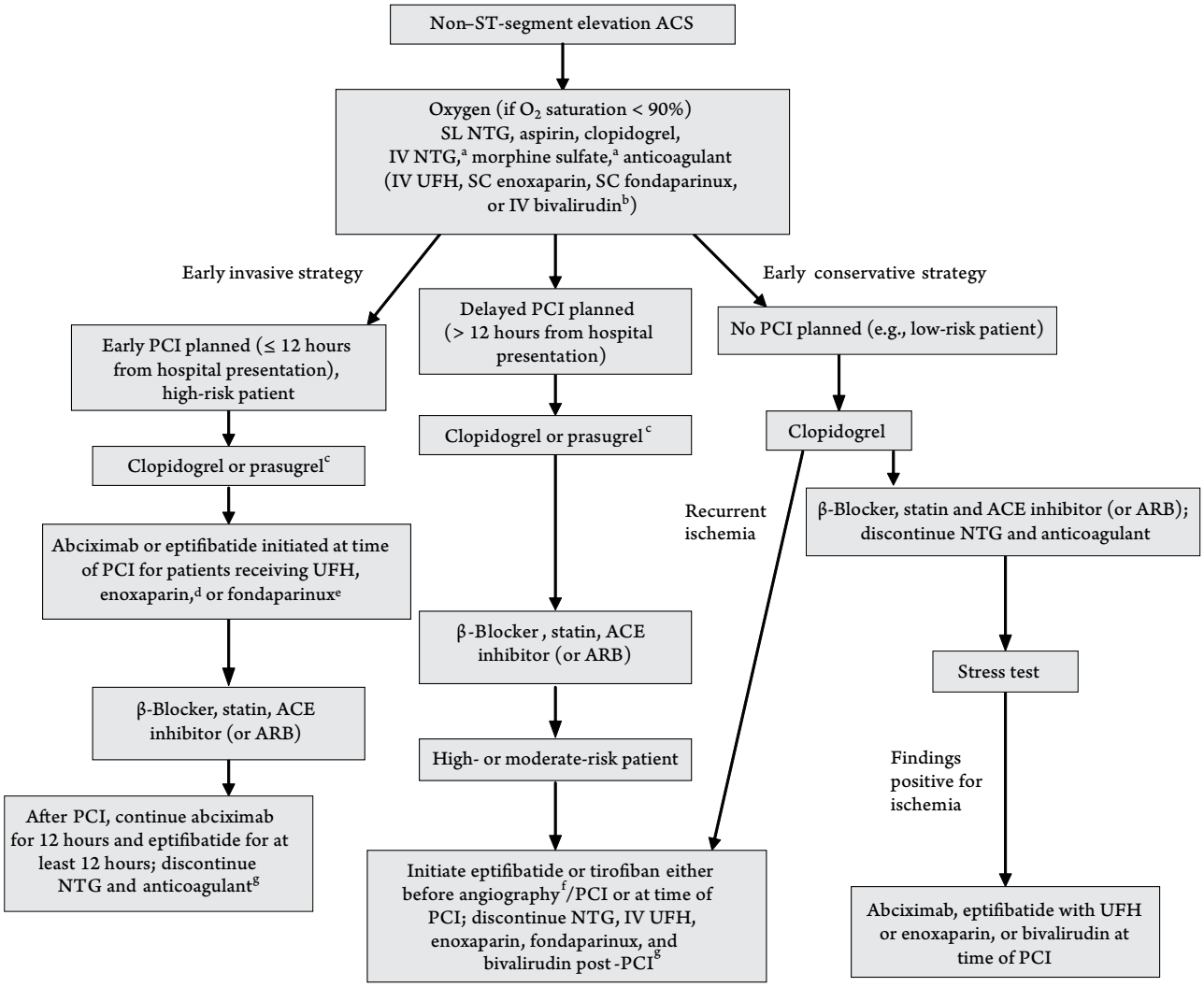

Figure 1-3. Initial treatment of non–ST-segment elevation ACS.

[a]For selected patients, see Table 1-2.
[b]Enoxaparin, UFH, fondaparinux (plus UFH added at time of PCI), or bivalirudin for early invasive strategy or delayed PCI strategy; enoxaparin or fondaparinux if no angiography/PCI planned; fondaparinux or bivalirudin preferred if high risk of bleeding; UFH preferred if patients going for CABG.
[c]In patients unlikely to undergo CABG; initiate prasugrel at time of PCI.
[d]May require an IV supplemental dose of enoxaparin; see Table 1-2.
[e]May require an IV supplemental dose of UFH; see Table 1-2.
[f]For signs and symptoms of recurrent ischemia.
[g]SC enoxaparin or UFH can be continued at a lower dose for venous thromboembolism prophylaxis.
ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; IV = intravenous; NTG = nitroglycerin; PCI = percutaneous coronary intervention; SC = subcutaneous; SL = sublingual; UFH = unfractionated heparin.

Table 1-2. Evidence-Based Pharmacotherapy for ST-segment Elevation and Non–ST-segment Elevation ACSs

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy
Aspirin	STEMI, Class I recommendation for all patients NSTE ACS, Class I recommendation for all patients	Hypersensitivity, active bleeding, severe bleeding risk	160–325 mg orally once on hospital day 1 75–162 mg orally once daily starting hospital day 2 and continued indefinitely in patients not receiving an intracoronary stent 162–325 mg orally once daily for a minimum of 30 days in patients undergoing PCI receiving a bare metal stent, 3 months with a sirolimus-eluting stent, and 6 months with a paclitaxel-eluting stent, followed by 75–162 mg orally once daily thereafter Continue indefinitely
Clopidogrel	NSTE ACS, Class I recommendation added to aspirin STEMI, Class I recommendation added to aspirin PCI in STE and NSTE ACS, Class I recommendation In patients with aspirin allergy, Class I recommendation	Hypersensitivity, active bleeding, severe bleeding risk	300-mg (Class I recommendation) to 600-mg (Class IIa recommendation) oral loading dose on hospital day 1 followed by a maintenance dose of 75 mg once daily starting on hospital day 2 in patients with NSTE ACS. In patients with NSTE ACS selected for an early invasive strategy, administer clopidogrel before or at time of PCI (Class I recommendation) and prasugrel at time of PCI (Class I recommendation) 300-mg oral loading dose followed by 75 mg orally daily in patients receiving a fibrinolytic or patients with a STEMI who do not receive reperfusion therapy (avoid loading dose in patients aged ≥ 75 years) 300–600 mg (Class I recommendation) loading dose before or when primary PCI performed Discontinue at least 5 days before elective CABG surgery (Class I recommendation) Administer indefinitely in patients with aspirin allergy (Class I recommendation) Continue for at least 12 months (Class I recommendation) and up to 15 months (Class IIb recommendation) in patients with ACS managed wit PCI/stent In patients receiving a fibrinolytic or that do not receive reperfusion therapy in patients with a STEMI, administer for at least 14 days (Class I) and up to 1 year (Class IIa)
Prasugrel	PCI in STE and NSTE ACS, added to aspirin (Class I recommendation)	Active bleeding, prior stroke, or prior TIA	Initiate in patients with known coronary artery anatomy only (to avoid use in patients needing CABG surgery) (Class I recommendation) Avoid in patients ≥ 75 years old unless DM or history of MI 60-mg oral loading dose followed by 10 mg once daily for patients weighing ≥ 60 kg 60-mg oral loading dose followed by 5 mg once daily for patients weighing < 60 kg Discontinue at least 7 days before elective CABG surgery (Class I recommendation) Continue for at least 12 months (Class I recommendation) and up to 15 months (Class IIb recommendation) in patients with ACS managed wit PCI/stent
Unfractionated heparin	STEMI, Class I recommendation in patients undergoing PCI and for patients treated with fibrinolytics; Class IIa recommendation for patients not treated with fibrinolytic therapy NSTE ACS, Class I recommendation in combination with antiplatelet therapy for conservative or invasive approach PCI, Class I recommendation (NSTE ACS and STEMI)	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke	For STEMI with fibrinolytics, administer heparin 60 units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour) For STEMI primary PCI, administer a 50- to 70-unit/kg IV bolus if a GPIIb/IIIa inhibitor planned; or 70- to 100-units/kg IV bolus if no GPIIb/IIIa inhibitor planned and supplement with IV bolus doses to maintain target ACT For NSTE ACS, administer a 60-unit/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour) Titrated to maintain an aPTT of 1.5–2.0 times control (about 50–70 seconds) for STEMI with fibrinolytics and for NSTE ACS Titrated to ACT of 250–350 seconds for primary PCI without a GP IIb/IIIa inhibitor and 200–250 seconds in patients given a concomitant GP IIb/IIIa inhibitor The first aPTT should be measured at 4–6 hours for NSTE ACS and STE ACS in patients *not* treated with fibrinolytics or undergoing primary PCI The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with fibrinolytics Continue for 48 hours or until the end of PCI
Enoxaparin	STEMI Class I recommendation in patients receiving fibrinolytics; Class IIa recommendation for patients not undergoing reperfusion therapy NSTE ACS, Class I recommendation in combination with aspirin for conservative or invasive approach For PCI, Class IIa recommendation as alternative to UFH in patients with NSTE ACS For primary PCI in STEMI, Class IIb recommendation as alternative to UFH	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke Avoid enoxaparin if CrCl < 15 mL/minute Avoid if CABG surgery planned	Enoxaparin 1 mg/kg SC every 12 hours for patients with NSTE ACS (CrCl ≥ 30 mL/minute) Enoxaparin 1 mg/kg SC every 24 hours (CrCl 15–29 mL/minute) for NSTE or STEMI For all patients undergoing PCI after initiation of SC enoxaparin for NSTE ACS, a supplemental 0.3-mg/kg IV dose of enoxaparin should be administered at the time of PCI if the last dose of SC enoxaparin was given 8–12 hours before PCI For patients with STEMI receiving fibrinolytics: • Age < 75 years: administer enoxaparin 30 mg IV bolus followed immediately by 1 mg/kg SC every 12 hours (first two doses administer maximum of 100 mg for patients for weighing more than 100 kg) • Age ≥ 75 years: administer enoxaparin 0.75 mg/kg SC every 12 hours (first two doses administer maximum of 75 mg for patients weighing more than 75 kg) Continue throughout hospitalization or up to 8 days for STEMI Continue for 24–48 hours for NSTE ACS or until the end of PCI
Bivalirudin	NSTE ACS Class I recommendation for invasive strategy PCI in STEMI (Class I recommendation)	Active bleeding, severe bleeding risk	For NSTE ACS, administer 0.1-mg/kg IV bolus followed by 0.25-mg/kg/hour infusion For PCI in NSTE ACS, administer a second bolus 0.5 mg/kg IV and increase infusion rate to 1.75 mg/kg/hour For PCI in STEMI, administer 0.75 mg/kg IV bolus followed by 1.75 mg/kg/hr infusion If prior UFH given, discontinue UFH and wait 30 minutes before initiating bivalirudin Dosage adjustment for renal failure: none required in the HORIZONS-AMI trial Discontinue at end of PCI or continue at 0.25 mg/kg/hr if prolonged anticoagulation necessary

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Table 1-2. Evidence-Based Pharmacotherapy for ST-segment Elevation and Non–ST-segment Elevation ACSs *(Continued)*

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy
Fondaparinux	Class I recommendation for STEMI receiving fibrinolytics; Class IIa recommendation for patients not undergoing reperfusion therapy Class I for NSTE ACS for invasive or conservative approach	Active bleeding, severe bleeding risk, SCr ≥ 3.0 mg/dL, or CrCl < 30 mL/minute	For STEMI, 2.5-mg IV bolus followed by 2.5 mg SC once daily starting on hospital day 2 For NSTE ACS, 2.5 mg SC once daily For PCI, give 50–60 units/kg IV bolus of UFH (regimen not rigorously studied); continue until hospital discharge or up to 8 days
Fibrinolytic therapy	STEMI, Class I recommendation for patients presenting within 12 hours after the onset of symptoms; Class IIa recommendation in patients presenting between 12 hours and 24 hours after the onset of symptoms with continuing signs of ischemia NSTE ACS, Class III recommendation	Any prior intracranial hemorrhage Known structural cerebrovascular lesions (e.g., arterial venous malformation) Known intracranial malignant neoplasm Ischemic stroke within 3 months Active bleeding (excluding menses) Significant closed head or facial trauma within 3 months	Streptokinase: 1.5 million units IV over 60 minutes Alteplase: 15-mg IV bolus followed by 0.75 mg/kg IV over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg (maximum 35 mg) over 60 minutes (maximal dose = 100 mg) Reteplase: 10 units IV bolus followed 30 minutes later by second IV bolus of 10 units Tenecteplase: • < 60 kg = 30-mg IV bolus • 60–69.9 kg = 35-mg IV bolus • 70–79.9 kg = 40-mg IV bolus
Glycoprotein IIb/IIIa receptor inhibitors	NSTE ACS, Class IIa recommendation for either tirofiban or eptifibatide for patients with continuing ischemia, elevated troponin, or other high-risk features; Class I recommendation for patients undergoing PCI; Class IIb recommendation for patients without high-risk features who are not undergoing PCI STEMI, Class IIa recommendation for primary PCI	Active bleeding, thrombocytopenia, prior stroke, renal dialysis (eptifibatide)	**Drug** / **Dose for STEMI PCI** / **Dose for NSTE ACS with/without PCI** / **Dose adjustment for renal insufficiency** Abciximab: 0.25-mg/kg IV bolus followed by 0.125 mcg/kg/minute (maximum10 mcg/minute) for 12 hours / Not recommended / None Eptifibatide: 180-mcg/kg IV bolus with an infusion of 2 mcg/kg/minute followed 10 minutes later by second IV bolus of 180-mcg/kg started after the first bolus and continued for up to 12–18 hours after PCI / 180-mcg/kg IV bolus followed by an infusion of 2 mcg/kg/minute for 12–72 hours / Reduce maintenance infusion to 1 mcg/kg/minute for patients with CrCl < 50 mL/minute; not studied in patients with SCr > 4.0 mg/dL Patients weighing 121 kg or more should receive a maximal infusion rate of 22.6 mg per bolus and a maximal infusion rate of 15 mg/hour Tirofiban: 25 mcg/kg IV bolus followed by an infusion of 0.1 mcg/kg/minute for up to 18 hours / 0.4-mg/kg IV bolus administered over 30 minutes followed by an infusion of 0.1 mcg/kg/minute for 18–72 hours / Reduce maintenance infusion to 0.05 mcg/kg/minute for patients with CrCl < 30 mL/minute
Nitroglycerin	STEMI and NSTE ACS, Class I indication in patients with continuing ischemic discomfort, control of hypertension, or management of pulmonary congestion	Hypotension, sildenafil, or vardenafil within 24 hours or tadalafil within 48 hours	0.4 mg SL, repeated every 5 minutes times three doses 5- to 10-mcg/minute IV infusion titrated up to 75–100 mcg/minute until relief of symptoms or limiting adverse effects (headache) with a systolic blood pressure < 90 mm Hg or more than 30% below starting mean arterial pressure levels if significant hypertension is present Topical patches or oral nitrates are acceptable alternatives for patients without continuing or refractory symptoms Continue IV infusion for 24–48 hours
β-Blockers[c]	STEMI and NSTE ACS, Class I recommendation for oral β-blockers in all patients without contraindications in the first 24 hours; Class IIa for IV β-blockers in patients with hypertension	PR ECG segment > 0.24 sec, 2nd degree or 3rd degree atrioventricular heart block Pulse rate < 60 beats/minute, systolic blood pressure < 90 mm Hg, shock, left ventricular failure with congestive symptoms Severe reactive airway disease	Target resting pulse rate of 50–60 beats/minute Metoprolol 5-mg slow IV push (over 1–2 minutes), repeated every 5 minutes for a total of 15 mg followed in 1–2 hours by 25–50 mg by mouth every 6 hours; if a very conservative regimen is desired, initial doses can be reduced to 1–2 mg Propranolol 0.5- to 1-mg IV dose followed in 1–2 hours by 40–80 mg by mouth every 6–8 hours Atenolol 5-mg IV dose followed in 5 minutes by a second 5-mg IV dose for a total of 10 mg followed in 1–2 hours by 50–100 mg orally once daily Alternatively, initial IV therapy can be omitted Continue oral β-blocker indefinitely

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Table 1-2. Evidence-Based Pharmacotherapy for ST-segment Elevation and Non–ST-segment Elevation ACSs *(Continued)*

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy
Calcium channel blockers	STEMI Class IIa recommendation and NSTE ACS Class I recommendation for patients with continuing ischemia who are already taking adequate doses of nitrates and β-blockers or in patients with contraindications to or intolerance of β-blockers (diltiazem or verapamil preferred during initial presentation) NSTE ACS, Class IIb recommendation for diltiazem for patients with AMI	Pulmonary edema, evidence of left ventricular dysfunction Systolic blood pressure < 100 mm Hg, PR ECG segment > 0.24 second for verapamil and diltiazem 2nd- or 3rd-degree atrioventricular heart block for verapamil or diltiazem Pulse rate < 60 beats/minute for diltiazem or verapamil	Diltiazem 120–360 mg sustained release orally once daily Verapamil 180–480 mg sustained release orally once daily Nifedipine 30–90 mg sustained release orally once daily Amlodipine 5–10 mg orally once daily Continue indefinitely if contraindication to oral β-blocker persists
ACE inhibitors	NSTE ACS or STEMI, Class I recommendation for patients with heart failure, left ventricular dysfunction and EF ≤ 40%, type 2 DM, or chronic kidney disease in the absence of contraindications Consider in all patients with CAD (Class I recommendation, Class IIa in low-risk patients) Indicated indefinitely for all patients with EF < 40% (Class I recommendation)	Systolic blood pressure < 100 mm Hg, history of intolerance to an ACE inhibitor, bilateral renal artery stenosis, serum potassium > 5.5 mEq/L, acute renal failure, pregnancy	Drug / Initial dose (mg) / Target dose Captopril / 6.25–12.5 / 50 mg twice daily orally to 50 mg three times daily Enalapril / 2.5–5.0 / 10 mg orally twice daily Lisinopril / 2.5–5.0 / 10–20 mg orally once daily Ramipril / 1.25–2.5 / 5 mg twice daily or 10 mg once daily orally Trandolapril / 1.0 / 4 mg once daily orally
Angiotensin receptor blockers	NSTE MI or STEMI, Class I recommendation in patients with clinical signs of heart failure or left ventricular EF < 40% and intolerant of an ACE inhibitor; Class IIa recommendation in patients with clinical signs of heart failure or EF < 40% and no documentation of ACE inhibitor intolerance Class I in other intolerant patients with hypertension	Systolic blood pressure < 100 mm Hg, bilateral renal artery stenosis, serum potassium > 5.5 mg/dL, acute renal failure, pregnancy	Drug / Initial dose (mg) / Target dose Candesartan / 4–8 / 32 mg orally once daily Valsartan / 40 / 160 mg orally twice daily Continue indefinitely
Aldosterone antagonists	STE ACS, Class I recommendation for patients with MI and EF ≤ 40% and either DM or heart failure symptoms who are already receiving an ACE inhibitor	Hypotension, hyperkalemia, serum potassium > 5.0 mEq/L, SCr > 2.5 mg/dL and/or CrCl < 30 mL/minute	Drug / Initial dose (mg) / Target dose Eplerenone / 25 / 50 mg orally once daily Spironolactone / 12.5 / 25–50 mg orally once daily Continue indefinitely
Morphine sulfate	STE and NSTE ACS, Class I recommendation for patients whose symptoms are not relieved after three serial SL nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension, respiratory depression, confusion, obtundation	2- to 4-mg IV bolus dose May be repeated every 5–15 minutes as needed to relieve symptoms and maintain patient comfort

[a]Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II recommendations are conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa recommendations, the weight of the evidence/opinion is in favor of usefulness/efficacy. Class IIb recommendations are those for which usefulness/efficacy is less well established by evidence/opinion. Class III recommendations are those in which the procedure or treatment is not useful and may be harmful.

[b]Allergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

[c]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance because of existing pulmonary disease (especially asthma), selection should favor a short-acting agent such as propranolol or metoprolol or the ultra short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg of IV metoprolol, 12.5 mg of oral metoprolol, or 25 mcg/kg/minute of esmolol as initial doses) rather than complete avoidance of β-blocker therapy.

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ACT = activated clotting time; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; AHA = American Heart Association; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CrCl = creatinine clearance; DM = diabetes mellitus; ECG = electrocardiogram; EF = ejection fraction; HORIZONS-AMI = Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; IV = intravenous; MI = myocardial infarction; NSTE = non–ST-segment elevation; PCI = percutaneous coronary intervention; SC = subcutaneous; SCr = serum creatinine; SL = sublingual; STE = ST-segment elevation; TIA = transient ischemic attack.

Table 1-3. Pharmacokinetics of Clopidogrel and Prasugrel

	Prasugrel	Clopidogrel
Absorption and metabolism	Prodrug	Prodrug
	Active metabolite R-138727	Inactive metabolite SR266334
		Active metabolite R-130946
	Metabolism to R-138727 is primarily by CYP3A4 and CYP2B6	Metabolism to R-130946 is primarily by CYP3A4, CYP2B6, and CYP1A2, with lesser contributions from CYP2C9 and CYP2C19
	Exposure to the active metabolite is not affected by *CYP2C19* and *CYP2C9* polymorphism	Exposure to the active metabolite is affected by CYP 2C19, 2C9, and ATP-binding cassette B1 *(ABCB1)* transporter (also called P-glycoprotein) polymorphism
	Rapid conversion of the parent drug to active metabolite (median time to peak plasma concentration of active metabolite ≈30 minutes)	Rapid conversion of the parent drug to active metabolite (mean time to peak plasma concentration of active metabolite ≈1 hour)
Food effect	Fasting administration preferred; C_{max} is reduced by 49% and t_{max} delayed 0.5–1.5 hours when administered with high-fat, high-calorie meal, although AUC is unaffected	One report in healthy volunteers of bioavailability of inactive metabolite concentrations unaffected by food; one report in healthy volunteers of clopidogrel t_{max} delayed by 1.5 hours, C_{max} increased 6-fold and bioavailability increased 9-fold
Disposition	Linear pharmacokinetics at doses up to 75 mg	Linear pharmacokinetics at doses of 50–150 mg
Elimination	Median elimination half-life of the active metabolite ≈7.4 hours	Elimination half-life of active metabolite not properly characterized, but reported to be a mean of 1.9 hours in one analysis
	Excretion is primarily urinary (≈70%); fecal excretion < 30%	Excretion is 50% urinary and 46% fecal
Labeled drug interactions	Enhanced bleeding with warfarin and NSAIDs	Enhanced bleeding with warfarin and NSAIDs
		Reduced active metabolite and antiplatelet effect with inhibitors of CYP2C19 (e.g., omeprazole)
		Adminstration of clopidogrel with agents known to inhibit CYP2C19 should be avoided (e.g., omeprazole, esomeprazole, cimetidine, fluconazole, ketokonazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, ticlopidine)

AUC = area under the curve; CYP = cytochrome P450; NSAIDs = nonsteroidal anti-inflammatory drugs.

Myocardial Damage During Angioplasty (ARMYDA)-5 trial. Researchers evaluated optimal timing of clopidogrel in the setting of diagnostic angiography in patients with either stable angina or NSTE ACS. Study arms included (1) clopidogrel pretreatment 6 hours before angiography and (2) ad hoc clopidogrel only for patients who underwent PCI while in the catheterization laboratory. There was no significant difference in the primary end point of death, MI, or target-vessel revascularization, and no bleeding events occurred; however, the study was likely underpowered for such events, with only 175 patients in each arm. There were no differences in periprocedural MI even though the pretreatment arm had a higher percentage of platelet aggregation inhibition at the time of PCI, as well as 2 hours after PCI, compared with the ad hoc group. At 6 hours after PCI, there were no significant differences in platelet aggregation between groups. This study was presented in late 2007 but has not yet been published. Other studies evaluating the timing of clopidogrel administration are continuing, including a study comparing prehospital versus in-hospital administration for patients with STEMI.

On the basis of available data and 2009 ACC/AHA PCI guideline recommendations, clopidogrel 300–600 mg should be administered as soon as possible in patients undergoing primary PCI. For those with STEMI receiving fibrinolytics, dosing according to the 2007 and 2009 ACC/AHA STEMI guideline update as described above and in Table 1-2 is recommended. For patients with NSTE ACS, debate exists about how early clopidogrel should be administered, either in the emergency department or after angiography when coronary anatomy has been determined and patients needing CABG surgery can be excluded.

Although data from CURE suggest that benefit is seen within the first 24 hours, the question remains whether the precise timing of clopidogrel administration for all patients with NSTE ACS (i.e., very early at time of emergency department presentation vs. preprocedural before a schedule angioplasty vs. ad hoc based on the coronary anatomy just before PCI) is critical to outcome.

Prasugrel

Prasugrel is a third-generation thienopyridine prodrug that inhibits platelet aggregation by blocking adenosine diphosphate (ADP)-induced platelet activation through the P2Y12 receptor. The first-generation agent ticlopidine is rarely used because of the significant risk of drug-induced neutropenia (2.4%) and agranulocytosis (0.8%); these require biweekly complete blood cell counts for the first 3 months of therapy. Like the second-generation thienopyridine clopidogrel, prasugrel is a prodrug; however, it has a more rapid onset of action and a greater degree of platelet inhibition after either a loading dose (60 mg of prasugrel vs. 600 mg of clopidogrel) or a once-daily maintenance dose (10 mg of prasugrel vs. 75 mg of clopidogrel).

The pharmacokinetics of prasugrel and clopidogrel are compared in Table 1-3. Prasugrel is hydrolyzed to the thiolactone R-95913 through hydrolysis by carboxylesterases. An inactive metabolite, R-95913 is then oxidized to the active metabolite R-138727, primarily by CYP3A4 and CYP2B6 and, to a lesser extent, by CYP2C19 and CYP2B6. Additional in vitro data indicate that the conversion of R-95913 to R-138727 occurs just as efficiently with CYP3A5 as with CYP3A4, suggesting that prasugrel could have a lower likelihood of significant interaction with CYP3A4 inhibitors.

In contrast, about 85% of an administered dose of clopidogrel is inactivated through ester hydrolysis by human carboxylesterase to the inactive metabolite SR-26334, resulting in less availability of the active metabolite R-130946. The active metabolite is produced from the parent compound in a two-step process through metabolism by CYP1A2, CYP2C19, and CPY2B6 to 2-oxo-clopidogrel and then to the active metabolite through CYP3A4, CYP2C9, CYP2C19, and CYP2B6.

Genetic variants in *CYP2C19* genes have been shown to affect the antiplatelet response to clopidogrel but not to prasugrel. Diminished metabolism of clopidogrel to its active metabolite, resulting in an attenuated antiplatelet response, has been shown for patients taking clopidogrel who have at least one mutant allele of the *CYP2C19* 681G>A loss-of-function polymorphism, most often the *2 allele. Genetic variation in *CYP3A4, CYP2B6,* and *CYP2C19* has no significant effect on prasugrel pharmacokinetics or antiplatelet response. No clinically significant drug interactions were seen when prasugrel was coadministered with the CYP2B6 substrate bupropion; with the CYP3A4, CYP2C19, and CYP2C8 inducer rifampin; or with the CYP3A4 substrate ketoconazole.

No significant interaction between prasugrel and atorvastatin was shown in a single published pharmacokinetic and pharmacodynamic study of healthy subjects. However, in another pharmacokinetic study, one case of acute liver injury was reported. The patient developed elevations in liver transaminases of less than 3 times the upper limit of the normal range after 7 days of atorvastatin; this increased to more than 3 times the upper limit of normal 3 days after the addition of prasugrel and resolved 56 days after cessation of prasugrel and atorvastatin. Unlike clopidogrel, prasugrel has no clinically significant interactions with any proton pump inhibitor. Prasugrel is not an inhibitor of P-glycoprotein (P-GP), as shown by a lack of interaction with digoxin. Therefore, clopidogrel has a higher rate of genetically associated nonresponsiveness, and prasugrel has a lower potential for drug-drug interactions.

Prasugrel was compared with clopidogrel in the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel (TRITON)-TIMI 38. This trial enrolled 13,608 patients with moderate- to high-risk ACS and with scheduled PCI. Prasugrel (administered as a loading dose of 60 mg followed by a maintenance dose of 10 mg once daily) was superior to clopidogrel (administered as a loading dose of 300 mg followed by a maintenance dose of 75 mg once daily) at a median follow-up of 14.5 months. Prasugrel reduced the occurrence of the primary end point (i.e., combined outcome of death from CV causes, nonfatal MI, or nonfatal stroke) but was associated with increased risk of TIMI major bleeding (Figure 1-4 and Figure 1-5). The rate of life-threatening bleeding was also increased with prasugrel compared with clopidogrel.

In an exploratory post hoc analysis, TRITON-TIMI 38 identified three subgroups of patients in whom prasugrel was associated with no net clinical benefit or with net harm: (1) those with a history of stroke or transient ischemic attack; (2) those with body weight below 60 kg; and (3) patients 75 and older. In contrast, published analyses identify three subgroups of patients who show particular benefit and safety from prasugrel compared with clopidogrel. The frequency of the primary composite end point was lower, and the risk of TIMI major non-CABG bleeding was similar to clopidogrel in (1) patients with STEMI, (2) patients with diabetes mellitus (DM), and (3) patients with a stent. The number needed to treat (NNT) ranged from 21 in patients with DM to 50 in those undergoing PCI with stent placement (Figure 1-4). The number needed to harm (NNH), defined as major non-CABG surgical bleeding, was 167 in the main study (Figure 1-5), suggesting that prasugrel be considered a first-line antiplatelet agent in patients with ACS undergoing PCI.

Prasugrel was approved by the U.S. Food and Drug Administration (FDA) in July 2009. The drug is contraindicated in patients with a history of stroke or transient ischemic attack, and it carries a warning about increased bleeding risk in patients 75 years and older, patients

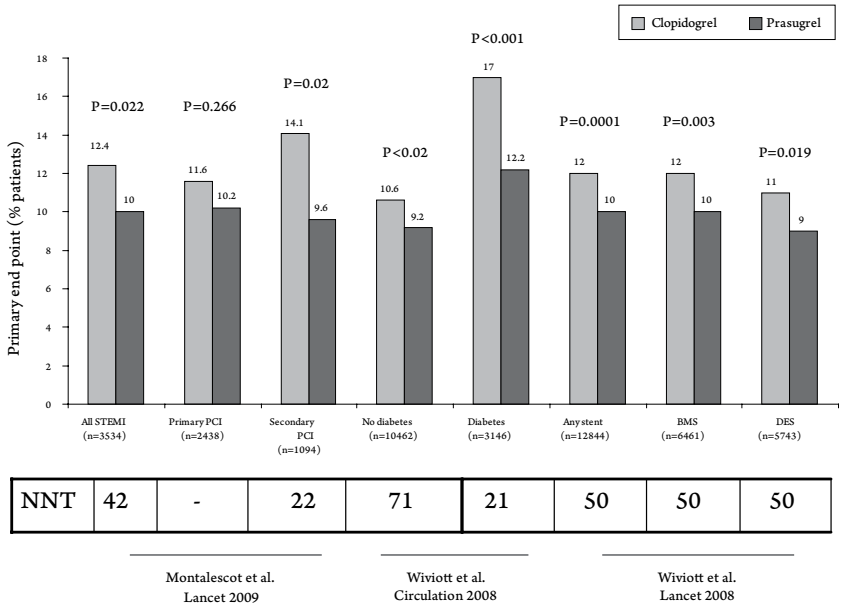

Figure 1-4. Cardiovascular death, myocardial infarction, or stroke in the TRITON-TIMI 38 trial.

BMS = bare metal stent; DES = drug-eluting stent; NNT = number needed to treat; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Revised with permission from Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. J Manag Care Pharm 2009;15:383–95.

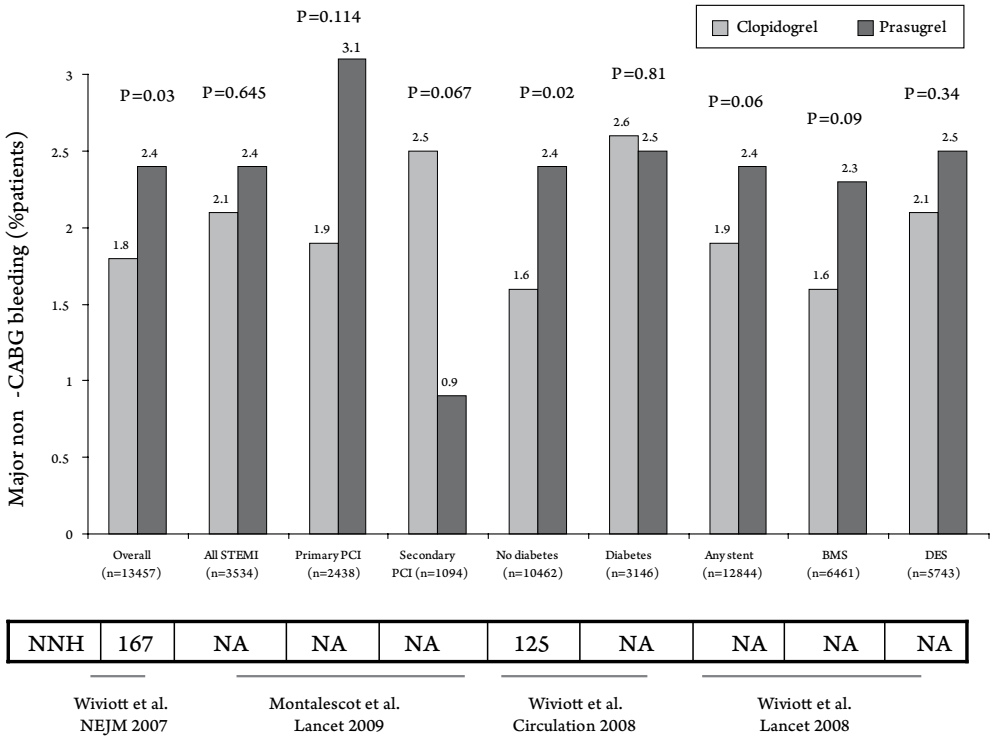

Figure 1-5. Major bleeding events in the TRITON-TIMI 38 trial.

BMS = bare metal stent; DES = drug-eluting stent; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Revised with permission from Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. J Manag Care Pharm 2009;15:383–95.

weighing less than 60 kg, and those undergoing surgical procedures (including CABG). Prasugrel's labeling requires that it be initiated in the hospital for treatment of ACS in patients undergoing PCI; its use is discouraged when the coronary anatomy is unknown and the possibility of CABG surgery has not been excluded. Prasugrel should be withheld at least 7 days before elective CABG surgery. There was no benefit, and there was increased risk of bleeding in patients 75 years or older in TRITON-TIMI 38; therefore, the product labeling recommends prasugrel in this age group only for a subgroup of patients likely to benefit from prasugrel compared with clopidogrel (i.e., those with either DM or prior MI).

Prasugrel has not been sufficiently studied in patients with significant hepatic or renal disease. Less than 1% of patients studied had a creatinine clearance estimated at less than 30 mL/minute, and only 10% had a creatinine clearance of 30–60 mL/minute. Because no data suggest that clopidogrel is safer in such a subgroup, either clopidogrel or prasugrel would be acceptable in the patient with chronic kidney disease. Patients receiving warfarin anticoagulation at baseline were not enrolled in TRITON-TIMI 38; therefore, the safety of prasugrel in patients receiving chronic anticoagulation is not established. Because there are published data associating bleeding risk with triple antithrombotic therapy using clopidogrel, aspirin, and warfarin, the author recommends clopidogrel over prasugrel in such patients.

No data are available to suggest that reducing the daily prasugrel maintenance dose from 10 mg to 5 mg results in a lower bleeding risk. The current TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial enrolled medically managed patients with recent NSTE ACS. Researchers will compare the rate of CV death, MI, or stroke between weight-adjusted prasugrel and standard clopidogrel groups after a minimal follow-up of 6 months. Depending on age and body weight, prasugrel is administered as either a 5-mg or 10-mg daily dose (with optional loading dose of 30 mg) and compared with clopidogrel 75 mg once daily (with optional loading dose of 300 mg). Current product labeling suggests a lower maintenance dose of prasugrel, 5 mg once daily, for patients weighing less than 60 kg. This is based on pharmacokinetic data suggesting increased active metabolite exposure with the 10 mg once-daily dose in such patients. Although not recommended in the product label, the TRITON-TIMI 38 study authors suggested that the maintenance dose of prasugrel be reduced to 5 mg daily in patients 75 and older.

The results of an economic substudy of TRITON-TIMI 38 indicate that the cost of treatment with prasugrel was similar to brand name clopidogrel ($26,067 vs. $26,288). Prasugrel treatment also resulted in 36 fewer re-hospitalizations for PCI compared with clopidogrel but at a cost of 11 hospitalizations for bleeding per 1000 patients treated.

The 2009 ACC/AHA STEMI update lists prasugrel as a class I recommendation for patients undergoing primary PCI or PCI in NSTE ACS (Table 1-2). As described above, the groups of patients likely to benefit from prasugrel is described in the text of the guideline; however, no recommendation is given over administration of clopidogrel, so either agent may be selected except where prasugrel is contraindicated. The timing of thienopyridine therapy was also recommended, with clopidogrel suggested to be administered at or before the time of PCI and prasugrel at the time of PCI.

Other P2Y12 Antagonists

Cangrelor

Cangrelor is an intravenous analog of adenosine triphosphate that inhibits the ADP P2Y12 receptor with rapid onset and rapid offset of antiplatelet effect. With a plasma half-life of 5–9 minutes, cangrelor achieves a high level of platelet inhibition (more than 90% with a 30-mcg/kg intravenous bolus followed by a 4-mcg/kg/minute infusion) within 5 minutes and reaches steady-state concentration within 15–30 minutes of administration.

Cangrelor is not a prodrug, and its major metabolite is inactive. Cangrelor is sequentially dephosphorylated to its nucleoside. In contrast with prasugrel and clopidogrel, cangrelor is rapidly reversible. After discontinuation of the intravenous infusion, platelet responsiveness to ADP-induced platelet aggregation is restored within 15 minutes. The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the P2Y12 receptor and prevents irreversible inhibition with prasugrel's and clopidogrel's active metabolite from occurring. This finding has been incorporated into clinical trials, with the conversion from cangrelor to clopidogrel occurring when the infusion is discontinued.

The results of two large phase III clinical trials evaluating cangrelor in PCI were published in late 2009. The CHAMPION PLATFORM trial was terminated prematurely by the Interim Analysis Review Committee for futility after enrolling about 83% of the planned 6400 patients. The trial compared the rate of mortality, MI, and ischemia-driven revascularization, as well as bleeding at 48 hours, between cangrelor and clopidogrel in patients with stable angina or NSTE ACS undergoing PCI. Patients with NSTE ACS had ischemic chest discomfort and either elevated troponin concentrations, indicating MI or had electrocardiographic changes and a history or DM and/or were older than 65 years. Patients were randomized to cangrelor, 30-mcg/kg intravenous bolus followed by an infusion of 4 mcg/kg/minute for 2 hours, or placebo started within 30 minutes of the procedure in clopidogrel-naïve patients. A clopidogrel 600-mg loading dose was administered at the end of the procedure to patients in the placebo group, followed by a maintenance dose of 75 mg daily. In the cangrelor group, clopidogrel administration was delayed until

the cangrelor infusion had been discontinued. At study closure, there was no significant difference in the primary end point between groups. The rate of stent thrombosis, a secondary end point, was significantly lower in cangrelor-treated patients; however the event rates were small: 5 patients in the cangrelor arm and 16 patients in the clopidogrel arm.

The CHAMPION PCI trial was also terminated prematurely by the Committee after enrolling 98% of the planned 9000 patients with stable angina, NSTE ACS, or STEMI undergoing PCI. The dose of cangrelor and clinical end points studied were the same as for CHAMPION PLATFORM. In CHAMPION PCI, the clopidogrel 600-mg loading dose was administered before the procedure in the placebo arm and at the end of the cangrelor infusion in the cangrelor arm. Cangrelor was not superior to placebo at either 48 hours or 30 days. In both CHAMPION PLATFORM and CHAMPION PCI, the incidence of TIMI major bleeding at 48 hours was low and did not differ between groups. Interestingly, the incidence of dyspnea was higher in cangrelor-treated patients. Because of cangrelor's unique pharmacokinetics, the continuing BRIDGE trial will evaluate the role of cangrelor as a bridge to CABG surgery after discontinuation of oral thienopyridine.

Ticagrelor

Ticagrelor, formerly called AZD6140, is an orally active reversible P2Y12 ADP receptor antagonist of a new class of antiplatelet agents termed *cyclopentyl-triazolo-pyrimidines*. Unlike prasugrel and clopidogrel, ticagrelor is not a prodrug; it binds directly to the P2Y12 receptor, with peak plasma concentrations achieved in 2–3 hours and a rapid onset of action of less than 2 hours. Its plasma half-life is 12 hours, and doses greater than 100 mg every 12 hours produce 90% or more platelet inhibition, which is greater platelet inhibition than clopidogrel 75 mg daily. The antiplatelet effects of ticagrelor dissipate to about 50% platelet inhibition at 24 hours post-dose. Ticagrelor is metabolized by CYP3A4 to an active metabolite, AR-C124910XX, which exhibits a peak concentration at 2 hours with about 35% of the parent compound's exposure and equal antiplatelet activity.

The Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non–ST-segment Elevation myocardial infarction (DISPERSE)-2 was a dose-ranging phase 2 safety trial. Researchers compared ticagrelor, either 90 mg or 180 mg twice daily, with clopidogrel 300-mg loading dose followed by 75 mg once daily for up to 3 months in 990 patients hospitalized with NSTE ACS symptoms for less than 48 hours. Patients in the ticagrelor arm were sub-randomized to receive an initial loading dose of 270 mg of ticagrelor or placebo. No significant differences were observed in major or minor bleeding events through 4 weeks.

In a platelet aggregation substudy of DISPERSE-2, ticagrelor showed rapid antiplatelet effects with more than 80% inhibition within 2.5 hours in the loading dose and the 180-mg dose groups. Two unanticipated adverse effects that emerged from early trials were acute dyspnea and heart block. Dyspnea occurred significantly more often in patients receiving the 180-mg twice-daily dose of ticagrelor than in patients receiving clopidogrel (15.8% vs. 6.4%) and was also reported in 10.5% of patients receiving 90 mg twice daily. Ventricular pauses of greater than 2.5 seconds occurred in almost 10% of patients in DISPERSE-2, with more than twice as many patients having three or more episodes of ventricular pauses in the ticagrelor 180-mg twice-daily group than in the clopidogrel treatment arm (4.9% vs. 2.0%).

The phase III PLATelet Inhibition and Patient Outcomes (PLATO) trial enrolled more than 18,000 patients with high-risk NSTE ACS or those undergoing PCI for STEMI. Researchers compared the rate of CV death, MI, or stroke, as well as major bleeding, between ticagrelor and clopidogrel. Ticagrelor was administered for 6–12 months (median study drug exposure was 277 days) as a 180 mg loading dose followed by 90 mg twice daily, with an additional 90 mg administered at the time of PCI. Clopidogrel was administered as a 300-mg loading dose with the option of an additional 300-mg dose administered at the time of PCI. Important exclusion criteria were patients at risk of bradycardia, patients receiving hemodialysis, those receiving strong inducers or inhibitors of CYP3A4, and those receiving CYP3A4 substrates with a narrow therapeutic window (e.g., cyclosporine).

Almost one-half of the patients in PLATO received open-label clopidogrel before randomized therapy, and significantly more patients randomized to ticagrelor discontinued the study drug (23.4% vs. 21.5%). At 12 months, ticagrelor significantly reduced the primary end point of MI and CV death by 16%. All-cause mortality was also significantly lower in ticagrelor-treated patients (4.5% vs. 5.9%). The reduction in CV death with ticagrelor was evident within the first 30 days as well as from days 1 to 360. Stent thrombosis was also lower in the ticagrelor group than in the clopidogrel group. Dyspnea occurred significantly more often in ticagrelor-treated patients (13.8% vs. 7.8% in the clopidogrel group), but few patients (0.9%) discontinued ticagrelor because of dyspnea.

In a subgroup of 2866 patients who underwent Holter monitoring, ventricular pauses of 3 seconds or longer were more common in ticagrelor-treated patients as well (2.1% vs. 1.7% in the clopidogrel group). As with prasugrel, increased efficacy came with a bleeding price. Both study-defined non-CABG major bleeding events and TIMI non-CABG major bleeding events were substantially increased in patients treated with ticagrelor.

In the subgroup of 13,408 patients specified by the investigator as intended for an invasive strategy, ticagrelor reduced the primary end point of CV death, MI or stroke, stent thrombosis, and all-cause mortality compared with clopidogrel without increasing either study-defined or

TIMI major bleeding. Therefore, ticagrelor appears to be a promising agent for treatment of ACS. However, the mechanisms of dyspnea and ventricular pauses remain to be fully described, and a plan for monitoring patients and more careful patient selection has not been proposed.

Newer Anticoagulants for ACS

Bivalirudin for STEMI

Bivalirudin is a short-acting, direct thrombin inhibitor that has been extensively studied in patients undergoing PCI. The results of the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial in patients with NSTE ACS were extensively reviewed in the PSAP-VI *Cardiology* book (2007).

More recently, bivalirudin has been studied in patients presenting with STEMI undergoing primary PCI. In the HORIZONS-AMI trial, 3602 patients with STEMI were randomized in a 2 by 2 manner to either open-label bivalirudin or unfractionated heparin (UFH) plus a GP IIb/IIIa inhibitor, in addition to aspirin and clopidogrel, with subrandomization to either a bare metal or paclitaxel-eluting intracoronary stent placement. A loading dose of clopidogrel 300 mg was used in about one-third of patients, with a 600-mg loading dose used in the rest. About 7.2% of patients in the bivalirudin group received ad hoc administration of a GP IIb/IIIa inhibitor for either the presence of thrombus or no reflow observed on coronary angiography.

Similar to other bivalirudin trials, the primary end point, a non-inferiority analysis, was a composite of net adverse clinical events (NACE) including recurrent ischemia (death, reinfarction, target-vessel revascularization for ischemia or stroke; collectively termed major adverse cardiac events [or MACE]) plus major bleeding not associated with CABG surgery. Bivalirudin significantly reduced the risk of the 30-day and 1-year NACE. These results were primarily driven by the reduction in major bleeding. Bivalirudin also reduced the risk of major bleeding when defined as TIMI major bleeding, but the difference in Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) life-threatening or severe bleeding was not significantly different between UFH plus GP IIb/IIIa inhibitor and bivalirudin. There was also no significant difference in the incidence of MACE, but no a priori non-inferiority margin was set for MACE in the pharmacology arm of the trial.

Although acute stent thrombosis occurring in the first 24 hours was higher in the bivalirudin-treated patients in HORIZONS-AMI, the risk of subacute stent thrombosis trended lower in these patients; thus, there was no significant difference between groups in stent thrombosis at 30 days. This may be in part attributable to the 30-minute gap in anticoagulation when patients were switched from prerandomized UFH to bivalirudin (66% of patients); UFH was discontinued 30 minutes before starting bivalirudin, as mandated by the protocol. Another factor may have been the short duration of bivalirudin administration just before and during PCI (lasting about 30–60 minutes during PCI, discontinued afterward) compared with GP IIb/IIIa inhibitors (12–18 hours) in the setting of no clopidogrel pretreatment. This is supported by the results of an exploratory subgroup analysis of clopidogrel dosing, which indicated that in bivalirudin-treated patients, the incidence of reinfarction was higher when a 300-mg clopidogrel dose was administered compared with a 600-mg dose.

In HORIZONS-AMI, major bleeding increased the risk of death, and in a post hoc analysis, bivalirudin significantly reduced the risk of all-cause mortality at 30 days and 1 year corresponding to its reduced bleeding risk compared with UFH plus a GP IIb/IIIa.

Therefore, consistent with the 2009 ACC/AHA STEMI guidelines, bivalirudin may be administered for primary PCI in patients presenting with STEMI who are also treated with aspirin and a loading dose of clopidogrel of 600 mg. Bivalirudin may be administered without delay as initial therapy, or patients may be switched to bivalirudin after initial treatment with UFH. Bivalirudin offers the advantage of a shorter duration of infusion and lower risk of major bleeding than UFH plus a GP IIb/IIIa inhibitor.

Economic analyses of HORIZONS-AMI are forthcoming. Given the results of both ACUITY and HORIZONS-AMI, the use of bivalirudin is increasing (was 11% in both NSTE MI and STEMI in the National Cardiovascular Data Registry Acute Coronary Treatment & Intervention Outcomes Registry – Get With the Guidelines [NCDR-ACTION GWTG]). However, there is still an important role for GP IIb/IIIa inhibitors in a significant portion of bivalirudin-treated patients who require provisional use of a GP IIb/IIIa inhibitor for thrombotic complications occurring during PCI.

Rivaroxaban

Rivaroxaban is an orally active oxazolidinone derivative that reversibly inhibits factor Xa. Unlike fondaparinux, which must bind to antithrombin III to inactivate factor Xa, rivaroxaban is a direct-acting competitive inhibitor inactivating both prothrombinase and clot-bound factor Xa. It has 80% bioavailability after a single oral dose, reaches peak plasma concentrations in 3 hours, and has a half-life in elderly patients of 11–13 hours. Rivaroxaban is 66% renally cleared, is a substrate for intestinal excretion through P-GP, and is metabolized to inactive metabolites by CYP3A4 and CYP2C8 oxidation and hydrolysis. Therefore, rivaroxaban should not be administered with strong inhibitors of CYP3A4 or P-GP (e.g., azole antifungals, ritonavir).

The administration of rivaroxaban with food increases the AUC and C_{max}, which in turn increases anti-factor Xa activity to 43% from 34% when given in the fasting state. For clinical trials in venous thromboembolism prophylaxis, rivaroxaban was administered within 2 hours of a meal. Rivaroxaban increases the prothrombin time and activated partial thromboplastin time transiently at peak effect; neither has been used for therapeutic drug monitoring

in clinical trials. There is no direct antidote, but administration of recombinant factor VIIa partially reverses rivaroxaban's effect. The drug offers the benefit of immediate anticoagulant effect without the necessity of coagulation test monitoring.

Studies of the addition of warfarin (international normalized ratio 2–3) to aspirin after MI have shown a reduction in reinfarction and stroke with increased risk of major bleeding. Thus, warfarin is only recommended after MI for patients at increased risk of stroke (e.g., a large amount of ventricular wall motion akinesis or dyskinesis) or with a chronic indication for anticoagulation (e.g., atrial fibrillation). There is also concern regarding the addition of clopidogrel or prasugrel to aspirin plus warfarin in patients requiring long-term anticoagulation because this triple antithrombotic combination has not been adequately studied in large-scale trials.

The Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome (ATLAS) TIMI-46 was a phase 2 dose-ranging trial of rivaroxaban in patients who had high-risk NSTE or STEMI within the past 7 days. The results, which were recently published, confirm concerns about bleeding risk when adding anticoagulation to dual antiplatelet therapy. The trial enrolled about 3500 patients with stabilized ACS who were hospitalized at least 1–7 days after either NSTE ACS or STEMI and were initially treated with aspirin. The patients were stratified into two groups based on concomitant use of clopidogrel (which was by physician preference) and then randomized to one of six rivaroxaban arms: 5 mg, 10 mg, or 20 mg once daily or 2.5 mg, 5 mg, or 10 mg twice daily for 6 months. The primary end points (i.e., TIMI major, TIMI minor, and bleeding defined as needing medical attention) were significantly higher in patients receiving rivaroxaban versus placebo. There was no significant difference between the primary composite efficacy end point, the incidence of death, MI, or ischemia requiring revascularization at 6 months, in the overall study cohort between rivaroxaban and placebo. A secondary composite end point, the incidence of death, MI, or stroke, was significantly lower with rivaroxaban compared with placebo; however, the benefit appeared to be confined to the group of patients not receiving clopidogrel.

A continuing phase III event-driven trial, ATLAS ACS TIMI 51, will enroll up to 16,000 patients with recent ACS (1–7 days post-event). This trial is comparing the rates of CV death, MI, or stroke between two rivaroxaban doses (2.5 mg twice daily and 5 mg twice daily) and placebo in addition to standard care (with clopidogrel treatment selected on physician preference). The expected duration of the study is 33 months, and results are expected in 2011. It remains to be determined whether the benefit of adding rivaroxaban to aspirin plus clopidogrel or aspirin plus prasugrel outweighs the risk of increased bleeding.

Rivaroxaban is approved in Europe as a 10-mg, once-daily dose for venous thromboembolism prevention. Rivaroxaban is contraindicated in patients with creatinine clearance less than 15 mL/minute, as well as patients receiving strong CYP3A4 and P-GP inhibitors (e.g., ketoconazole, HIV [human immunodeficiency virus] protease inhibitors). In addition to prevention and treatment of venous thromboembolism, rivaroxaban is being studied for stroke prevention in atrial fibrillation. Because of its rapid onset of anticoagulant effect, the drug may be considered for bridge therapy to warfarin, although no studies of that use have been reported.

Apixaban

Like rivaroxaban, apixaban is an orally available, direct-acting, reversible factor Xa inhibitor. In healthy volunteers, apixaban reaches peak plasma concentrations in 3 hours and has a half-life of 12 hours. Apixaban is metabolized by at least three pathways (*O*-demethylation, hydroxylation, and sulfation) and is, to a lesser extent, excreted renally. Like rivaroxaban, apixaban increases the prothrombin time and activated partial thromboplastin time in a concentration-dependent manner, but neither drug is used clinically for monitoring anticoagulant effect.

In a phase 2 dose-ranging study, apixaban 2.5 mg twice daily and 10 mg once daily were compared with placebo in 1246 patients with high-risk stabilized NSTE ACS or STEMI treated with aspirin and clopidogrel (by choice of the treating physician). The results showed the primary end point, the incidence of International Society of Thrombosis and Hemostasis major or clinically relevant non-major bleeding at 6 months, was more than 2-fold higher than placebo for patients treated with 10-mg once-daily apixaban. In both apixaban arms, patients receiving concomitant clopidogrel had higher bleeding rates than those not receiving clopidogrel.

Because there was a trend toward a lower composite ischemic outcome of CV death, MI, ischemic stroke, or severe recurrent ischemia in patients treated with 10 mg once daily of apixaban, a dose of 5 mg twice daily was chosen for the phase III trial Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE)-2. Of note, ischemic events were almost 2-fold higher in patients who did not receive clopidogrel. In APPRAISE-2, the frequency of CV death, MI or ischemic stroke, and bleeding will be compared between 5 mg of apixaban twice daily and placebo in patients with recent ACS. The primary advantage of these new anticoagulants is the lack of coagulation monitoring.

Quality Patient Care

Quality Metrics vs. Quality Performance Measures

During the past decade, there has been increased recognition that adherence to the ACC/AHA guideline recommendations for ACS results in lower patient mortality. These CV metrics (also called quality measures or

quality improvement measures) assess the quality of care and are a quality improvement target. They focus on the strongest recommendations from the guidelines such that failure to adhere to those measures results in poor patient outcomes.

Performance measures, a subset of quality metrics, are intended to be publicly reported, externally compared between institutions, and perhaps used by third-party payers in pay-for-performance considerations. Performance measures are developed through an extensive process of public comment, peer review, and ACC/AHA task force review. Test measures or candidate measures are quality metrics that do not meet criteria for a performance measure because they are not yet suitable for public reporting; these measures may still be of value to the hospital's quality improvement program or could evolve into a performance measure.

ACC/AHA 2008 STE and NSTE MI Performance Measures

The 2008 ACC/AHA quality performance measures and test measures for STEMI and NSTE MI are listed in Table 1-4. These measures differ from past measures (e.g., those described by the Joint Commission) in several ways. Because statin therapy initiation is recommended for all patients with ACS regardless of low-density lipoprotein cholesterol concentration, routine lipid panel assessment was changed from a performance to a test measure. Because routine administration of intravenous β-blockers to patients with tenuous hemodynamics was found to increase mortality in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), β-blocker administration on hospital arrival was deleted as a measure.

New performance measures tracking the times for interhospital transfer for primary PCI in patients with STEMI were added. Because exercised-based cardiac rehabilitation with risk factor management improves quality of life and reduces mortality after MI, referral to cardiac rehabilitation from the inpatient setting was added as a performance measure.

Excessive dosing of anticoagulants and GP IIb/IIIa inhibitors commonly occurs in patients with NSTE ACS and was associated with increased bleeding risk in the CRUSADE national quality improvement registry. Now, the ACC/AHA recommends anticoagulant dosing protocols (as do the American College of Chest Physicians guidelines) but goes a step further and recommends that ACS anticoagulant dosing errors be tracked in each hospital. These two recommendations are in agreement with the 2009 National Patient Safety Goals, which require hospitals to implement programs to improve medication safety. Guideline recommendations for heparin dosing for patients with NSTE ACS, STEMI treated with fibrinolytics, and STEMI undergoing primary PCI are listed in Table 1-2.

Finally, clopidogrel is recommended for all patients with STEMI and NSTE ACS, not just those undergoing

Table 1-4. ACC/AHA 2008 Quality Performance Measures and Test Measures for Myocardial Infarction

Quality Performance Measure	Test Measure
Aspirin at arrival	LDL-C assessment
Aspirin prescribed at discharge	Excessive initial heparin dose
β-Blocker prescribed at hospital discharge	Excessive initial LMWH dose
Statin prescribed at hospital discharge	Excessive initial abciximab dose
ACE inhibitor or ARB for LVD prescribed at discharge	Excessive initial eptifibatide dose
Evaluation of LV function	Excessive initial tirofiban dose
Time to fibrinolytic therapy for patients with STEMI or LBBB	Presence of an anticoagulation dosing protocol for ACS (structural measure)
Time to PCI for patient with STEMI	Presence of an anticoagulant medication error tracking system
Time from ED arrival to ED discharge when transferring for STEMI PCI to another hospital	
Time from ED arrival at STEMI referral facility to PCI at receiving facility	
Percentage of eligible patients with STEMI or LBBB receiving reperfusion therapy	
Smoking cessation counseling	
Cardiac rehabilitation referral	

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHA = American Heart Assocoation; ARB = angiotensin receptor blocker; ED = emergency department; LBBB = left bundle branch block; LDL-C = low-density lipoprotein cholesterol; LMWH = low-molecular-weight heparin; LVD = left ventricular dysfunction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

PCI and intracoronary stent placement. In the CURE trial, clopidogrel reduced the rate of death, MI, or stroke to a similar degree in both medically managed patients and those undergoing revascularization (19% vs. 17% reduction). In COMMIT, clopidogrel reduced the incidence of death, MI, or stroke in patients treated with fibrinolytics as well as those receiving medical management alone (11% vs. 6%) with no significant interaction in treatment effect. The rate of clopidogrel prescription is high on hospital discharge in patients undergoing PCI. However, data from the January 2007–June 2008 NCDR-ACTION GWTG indicate that clopidogrel was only prescribed to 56% of patients receiving medical management after NSTE MI. Therefore, clopidogrel prescription at hospital discharge is a test measure.

Participation in the NCDR-ACTION GWTG program may be used by institutions to track and evaluate their quality performance measures for ACS. Quarterly performance reports are intended to improve care provided by individual health care providers, hospitals, and health systems. Pharmacists play a key role in quality improvement by participating on hospital protocol and guideline writing committees, medication safety committees, and inpatient anticoagulation management teams; through the review and design of computer order entry sets; and by serving committees that track and respond to Joint Commission Core Measure success rates. Published examples of pharmacist-directed educational programs and protocols for improvements include reaching therapeutic activated partial thromboplastin times with heparin, treating patients with heparin-induced thrombocytopenia, and improving adherence to dose reduction guidelines for eptifibatide in patients with creatinine clearance greater than 50 mL/minute.

Estimating Bleeding Risk: The CRUSADE Bleeding Risk Score

Despite many different methods of measuring bleeding events, bleeding and transfusion during hospitalization of patients with ACS remain significant concerns. Many analyses of clinical trials in the past 5 years have linked the occurrence of in-hospital major bleeding events with increased mortality and reinfarction. Proposed mechanisms by which bleeding increases ischemic risk and mortality include coronary ischemia secondary to anemia with acute blood loss, prothrombotic effects secondary to activation of platelets and the coagulation cascade, premature discontinuation of anticoagulant and antiplatelet therapies, transfusion-associated proinflammatory response secondary to cytokine release, and hypoxia caused by storage-related *S*-nitrosohemoglobin deficiency of transfused blood products.

Risk factors for in-hospital bleeding complications in patients with ACS and in those undergoing PCI include older age, female sex, lower body weight, PCI, anemia, DM, and renal insufficiency. Recently, a bleeding risk score (Table 1-5) was developed to assist the clinician in

Table 1-5. CRUSADE Bleeding Risk Score

Predictor	Score
Baseline hematocrit (%)	
< 31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥ 40	0
Creatinine clearance (mL/min, Cockcroft-Gault formula)	
≤ 15	39
> 15–30	35
> 30–60	28
> 60–90	17
> 90–120	7
> 120	0
Pulse rate (beats/minute)	
≤ 70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥ 121	11
Sex	
Male	0
Female	8
Signs of heart failure at presentation	
No	0
Yes	7
Prior PAD or stroke	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure (mm Hg)	
≤ 90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥ 201	5

PAD = peripheral arterial disease.

evaluating in-hospital bleeding risk of patients with ACS. This risk assessment tool, the CRUSADE Bleeding Risk Score, was developed and validated using the NSTE MI subset of CRUSADE registry patients. The bleeding definition in this study was the CRUSADE major bleed, defined as an intracranial hemorrhage, retroperitoneal bleed, hematocrit drop of 12% or greater from baseline, any red blood cell transfusion when baseline hematocrit was 28% or greater, or any red blood cell transfusion when baseline hematocrit was less than 28%.

The CRUSADE independent predictors of major bleeding noted at admission are baseline hematocrit, estimated creatinine clearance, pulse rate, sex, signs of heart failure at presentation, history of peripheral arterial disease or stroke, DM, and systolic blood pressure. The predicted probability of in-hospital CRUSADE major bleeding by score is shown in Figure 1-6. Clinicians may use the CRUSADE bleeding risk score, adding up the point totals from each category, to assess a patient's bleeding risk and consider therapies associated with lower bleeding risk in patients with high risk scores. These therapies include radial versus femoral approach for cardiac catheterization, fondaparinux or bivalirudin compared with UFH or LMWH, more careful attention to dosing or possible avoidance of GP IIb/IIIa inhibitors, and more careful monitoring (e.g., more frequent complete blood cell counts). However, no prospective studies evaluating the use of the CRUSADE Bleeding Risk Score are available. Although long-term risks of bleeding are substantial with newer antiplatelets (e.g., prasugrel, ticagrelor) and anticoagulants (e.g., rivaroxaban, apixaban), no scales or scores have been developed to help identify individual patients at long-term risk of bleeding.

Conclusion

Anticoagulant and antiplatelet therapy for ACS are evolving. The ACC/AHA ACS and PCI guidelines are used by clinicians to establish protocols that improve adherence to guideline recommendations. Adherence to guideline recommendations results in lower mortality and reinfarction. Increased importance is placed on prevention of bleeding events in patients receiving antiplatelets and anticoagulants. The CRUSADE Bleeding Risk Score gives clinicians a tool to assist with risk estimation to better select and monitor therapy.

Quality metrics are at the forefront of care. New quality metrics focus on improving the safety of anticoagulation practices. Advances have occurred in antiplatelet and anticoagulant therapy. Prasugrel is clearly a more effective antiplatelet agent than clopidogrel; however, increased bleeding risk will require careful patient selection. Bivalirudin reduces bleeding events compared with enoxaparin and UFH. It remains to be established whether newer anticoagulants and antiplatelet agents such as cangrelor, ticagrelor, rivaroxaban, and apixaban will be superior to current agents while maintaining an acceptable safety profile.

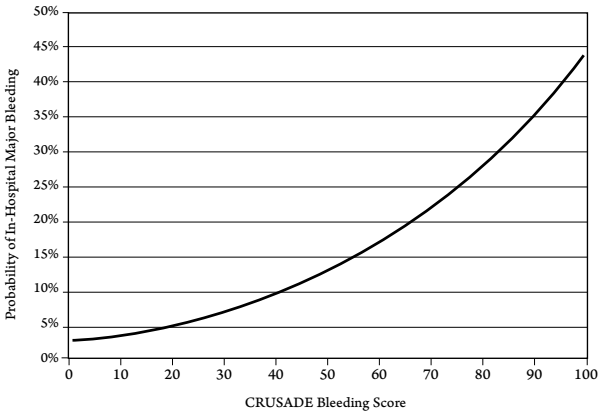

Figure 1-6. Predicted probability of CRUSADE in-hospital major bleeding according to CRUSADE Bleeding Risk Score.

Reprinted with permission of the American Heart Association. From Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009;119:1878.

Annotated Bibliography

1. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;20:2271–306.

   The ACC/AHA published an update to the STEMI and PCI guidelines in a single document in late 2009. Updates are intended to provide recommendation changes based upon new information. The original full guidelines for STEMI were published in 2004, and original full guidelines for PCI in 2005; updates for each were published in 2007. Therefore, recommendations covering STEMI and PCI (as described in Table 1-2) come from multiple documents. If a recommendation is not addressed in the 2009 update, it is intended that the reader refer back to the last update; if the recommendation is not there, the reader must referback to the full guidelines. This often confuses practitioners. The two major changes to drug therapy, namely recommendations surrounding the dosing and duration of thienopyridine use in STEMI and PCI, as well as a recommendation for bivalirudin in primary PCI, are described in detail in this chapter.

   Other recommendations include changing tirofiban and eptifibatide use in primary PCI from a grade IIb to IIa recommendation based upon the results of two meta-analyses of data comparing the small molecule agents tirofiban and

eptifibatide with abciximab; these suggested no differences in clinical end points. The Writing Committee did not recommend routine use of GP IIb/IIIa inhibitors in primary PCI, however, but rather selective use at the time of PCI in patients who have not received a thienopyridine or those patients in whom extensive intracoronary clot is observed.

Another recommendation pertaining to the use of insulin infusions is that intensive glucose control in STEMI (to less than 180 mg/dL) was changed from a class I recommendation (less than 160 mg/dL) to a class IIa recommendation. This came after the publication of a large randomized trial suggesting excess mortality in intensive care unit patients randomized to intensive glucose control to a goal of less than 180 mg/dL (time weighted average 115 mg/dL versus 144 mg/dL in the conventional glucose control group).

The guidelines also provide recommendations for triage and transfer from non-PCI-capable hospital to a PCI-capable hospital in patients who have received fibrinolytic therapy, as well as encouraging development of cooperative plans for early transfer for primary PCI between hospitals. The AHA has such a program, Mission Lifeline, designed to facilitate cooperation between institutions to reduce time delays for interhospital transfer.

2. Krumholz HM, Anderson JL, Bachelder BL, Fesmire FM, Fihn SD, Foody JM, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction) Developed in Collaboration With the American Academy of Family Physicians and American College of Emergency Physicians and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. Circulation 2008;118:2596–648.

These ACC/AHA guidelines define quality metrics as "measures that have been developed to support quality improvement at the provider, hospital and/or health-system level." Performance measures are the quality metrics deemed worthy of public reporting, according to the ACC/AHA Task Force on Performance Measures. Performance measures developed by ACC/AHA may be reviewed and endorsed by external agencies such as the Joint Commission, National Quality Forum, and Centers for Medicare and Medicaid Services. Performance measures are classified as diagnostics, patient education, treatment, self-management, or monitoring of disease states. The performance measures developed for MI were in the areas of diagnostics, patient education, and treatment. New quality metrics that have not undergone evaluation may be termed test measures (which ACC/AHA believes deserve further study); these are considered candidate measures that may eventually become performance measures. New test measures for MI in 2008 involved anticoagulant dosing and safety as well as GP IIb/IIIa inhibitor dosing.

3. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.

In the HORIZONS-AMI trial, bivalirudin was compared with UFH in patients undergoing primary PCI for STEMI. The dose of bivalirudin was 0.75 mg/kg intravenous bolus followed by an infusion of 1.75 mg/kg/hour. The dose of UFH was intravenous bolus 60 units/kg with subsequent boluses administered in the cardiac catheterization laboratory to achieve a target activated clotting time of 200–250 seconds. In most cases, bivalirudin and UFH were discontinued at the completion of the PCI. By design, a GP IIb/IIIa inhibitor (either eptifibatide or abciximab) was given to all patients receiving UFH. However, 7.2% of patients in the bivalirudin group also received a GP IIb/IIIa inhibitor during PCI secondary to the presence of either no flow or thrombus. Aspirin and a thienopyridine were administered to all patients before cardiac catheterization.

The two primary end points of this non-inferiority analysis were (1) the 30-day composite NACE including recurrent ischemia (death, reinfarction, target-vessel revascularization for ischemia, or stroke, collectively termed MACE) plus major bleeding not associated with CABG surgery and (2) major non-CABG bleeding. Bivalirudin significantly reduced the risk of the 30-day (9.2% vs. 12.1%, relative risk [RR] = 0.76, 95% confidence interval [CI], 0.63–0.92) and 1-year (15.7% vs. 18.3%, hazard ratio [HR] = 0.84, 95% CI, 0.71–0.98) NACE. These results were primarily driven by the reduction in major bleeding (4.8% vs. 8.3%, RR = 0.60, 95% CI, 0.46–0.77). Bivalirudin also reduced the risk of major bleeding when defined as TIMI major bleeding, but the difference in GUSTO life-threatening or severe bleeding was not significantly different between UFH plus GP IIb/IIIa inhibitor versus bivalirudin (0.6% vs. 0.4%, p=0.49). There was no significant difference in the frequency of MACE at 30 days (bivalirudin 5.4%, UFH plus a GP IIb/IIIa inhibitor 5.5%), but no a priori non-inferiority margin had been set for MACE in the pharmacology arm of the trial. The rates of MACE at 1 year were also not statistically different between bivalirudin and UFH plus a GP IIb/IIIa inhibitor (11.9% vs. 11.9%, HR = 1.00, p=0.98).

Bivalirudin showed an increased rate of early stent thrombosis, but it did not persist at either 30 days or 1 year. An increased dose of clopidogrel (600 mg rather than 300 mg) was associated with a reduced risk of acute stent thrombosis in bivalirudin-treated patients (1.3% vs. 2.8%, p=0.02) but not in those treated with UFH plus a GP IIb/IIIa inhibitor. This perhaps was because of the slightly earlier onset of effect of 600 mg versus 300 mg of clopidogrel and because the GP IIb/IIIa inhibitor was administered for at least 12 hours post-PCI, whereas bivalirudin was discontinued at the time of PCI. Therefore, the dose of clopidogrel used with bivalirudin for PCI should be 600 mg. Major bleeding was a predictor of increased risk of mortality (HR = 9.12, 95% CI, 5.73–14.52), and in a post hoc analysis, bivalirudin significantly reduced the risk of all-cause mortality at both 30 days (2.1% vs. 3.1%, p=0.049) and 1 year (3.45% vs. 4.8%, HR = 0.6971, 95% CI, 0.5051–0.98).

Because the drug acquisition costs of bivalirudin and eptifibatide are similar, with abciximab being more

expensive, and because there were fewer bleeding events and similar ischemic events in the two groups, a forthcoming economic analysis of HORIZONS-AMI at 1 year will likely favor bivalirudin. Bivalirudin in primary PCI is a class I recommendation for primary PCI in the ACC/AHA 2009 STEMI guideline update, with guidance on switching from UFH to bivalirudin at the time of PCI if desired (see Table 1-2).

4. APPRAISE Steering Committee and Investigators: Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877–85.

   The APPRAISE trial was a phase 2 dose-ranging study of apixaban, a direct-acting factor Xa inhibitor, in patients with recent (within 7 days) NSTE ACS or STEMI. Patients with severe renal insufficiency and those receiving strong CYP3A4 inhibitors were excluded. In phase A, 450 patients were randomized to either placebo or apixaban 2.5 mg twice daily or 10 mg once daily (added to standard therapy with aspirin and clopidogrel) for 30 days. Clopidogrel use was not mandated, but more than 75% of patients received aspirin plus clopidogrel at some point during the study. Once the safety of apixaban was ascertained by the independent monitoring committee, two additional higher doses were added to the study: (1) apixaban 10 mg twice daily and (2) apixaban 20 mg once daily. An additional 1265 patients were randomized to one of the four doses or placebo and observed for 26 weeks.

   The primary outcome of the study was International Society on Thrombosis & Haemostasis major bleeding (fatal, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, intramuscular with compartment syndrome, or pericardial bleeding or else bleeding associated with a decrease in hemoglobin of 2 g/dL or a transfusion of 2 or more units of packed red blood cells) and clinically relevant minor bleeding (non-major bleeding requiring medical or surgical intervention). The secondary outcome was the composite of CV death, MI, recurrent ischemia, or ischemic stroke. Most patients (63%) were enrolled after STEMI, whereas 30% had NSTE MI and 8% had unstable angina. The two higher-dose study arms were discontinued from the study prematurely because of excess major or minor bleeding rates of 24% in each group. Major and minor bleeding was higher in the apixaban 10-mg once-daily group compared with placebo (HR = 2.45, 95% CI, 1.31–4.61, p=0.005), and there was a trend toward higher bleeding rates in patients receiving apixaban 2.5 mg once daily (HR = 1.78, 95% CI, 0.91–3.48, p=0.09). Clopidogrel use increased the risk of bleeding with apixaban. The risk of ischemic events during 6 months was similar between the apixaban- and placebo-treated patients (HR = 0.73, 95% CI, 0.44–1.19, p=0.21 for apixaban 2.5 mg twice daily; and HR = 0.61, 95% CI, 0.35–1.04, p=0.07 with apixaban 10 mg once daily, compared with placebo). There was no difference in the incidence of liver toxicity between apixaban and placebo. A 5-mg twice-daily dose was selected to be compared with placebo in the APPRAISE-2.

5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

   The phase III, randomized, double-blind PLATO trial compared a ticagrelor 180-mg loading dose, followed by 90 mg twice daily, with a clopidogrel 300-mg loading dose, followed by 75 mg daily, in 18,624 patients with ACS. The primary efficacy end point was a composite of CV death, MI, or stroke at 12 months. The primary safety end point was PLATO-defined major bleeding; this was defined as life threatening if it was fatal, intracranial or intrapericardial or if it occurred with shock or hypotension requiring pressors or surgery, and it was defined as major "other" if it was not life threatening but was disabling. Of the patients enrolled, 16.6% had unstable angina, 42.9% had NSTEMI, and 37.5% had STEMI.

   Ticagrelor reduced the frequency of the composite end point CV death, MI, or stroke (9.8% vs. 11.7%, HR = 0.84, 95% CI, 0.77–0.92), as well as MI (5.8% vs. 6.9%, HR = 0.84, 95% CI, 0.75–0.85), stent thrombosis (2.9% vs. 3.8%, HR = 0.77, 95% CI, 0.62–0.95), CV death (4.0% vs. 5.1%, HR = 0.79, 95% CI, 0.69–0.91), and all-cause mortality (4.5% vs. 5.9%, HR = 0.78, 95% CI, 0.69–0.89). The PLATO-defined major bleeding was similar between ticagrelor and clopidogrel (11.6% vs. 11.2%, HR = 1.04, 95% CI, 0.95–1.13), as was TIMI major bleeding (7.9% vs. 7.7%, HR = 1.03, 95% CI, 0.93–1.15). However, PLATO-defined non-CABG major bleeding (4.5% vs. 3.8%, HR = 1.19, 95% CI, 1.02–1.38), as well as non-CABG TIMI major bleeding (2.8% vs. 2.2%, HR = 1.25, 95% CI, 1.02–1.53), was significantly higher with ticagrelor than with clopidogrel. The incidence of ventricular pauses of 3 seconds or greater was higher during the first week in patients treated with ticagrelor compared with clopidogrel (5.8% vs. 3.6%, p=0.01) but was not different at 30 days. Dyspnea occurred more with ticagrelor as well (13.8% vs. 7.8%, HR = 1.86, 95% CI, 1.68–2.02), but few patients discontinued ticagrelor versus discontinued clopidogrel because of dyspnea (0.9% vs. 0.1%, HR = 6.12, 95% CI, 3.41–11.01). Unlike prasugrel, there was no increased risk of stroke compared with clopidogrel.

   In the subgroup of 13,804 patients with intended early angiography and PCI, efficacy results mirrored the overall study with a significant reduction in CV death, MI, or stroke (9.0% vs. 10.7%, HR = 0.84, 95% CI, 0.75–0.94), MI (5.3% vs. 6.6%, HR = 0.80, 95% CI, 0.69–0.92), stent thrombosis (2.2% vs. 3.1%, HR = 0.72, 95% CI, 0.58–0.90), CV death (3.4% vs. 4.3%, HR = 0.82, 95% CI, 0.68–0.98), and all-cause mortality (3.9% vs. 5.1%, HR = 0.81, 95% CI, 0.68–0.95). However, there was no significant difference between ticagrelor and clopidogrel in PLATO-defined major bleeding (11.5% vs. 11.6%), TIMI major bleeding (8.0% vs. 8.0%), non–CABG PLATO-defined major bleeding (4.7% vs. 4.1%), or non-CABG TIMI major bleeding (2.8% vs. 2.3%). For every 1000 patients with ACS and an intended invasive treatment strategy, ticagrelor compared with clopidogrel resulted in 11 fewer deaths, 13 fewer MIs, and 6 fewer cases of stent thrombosis without any increase in bleeding events. It was estimated that six patients would

need to switch antiplatelet treatment to clopidogrel secondary to dyspnea.

Ticagrelor use requires careful monitoring for bradycardic events as well. Patients with severe kidney dysfunction were excluded from the trial, as were patients receiving concomitant therapy with strong CYP3A4 inhibitors or inducers. Drug interactions are likely to be more common with ticagrelor than with prasugrel. Because ticagrelor has a short half-life and a reversible antiplatelet effect, it would be preferred for patients likely to need CABG surgery: it need only be withheld for 3 days before surgery. However, because twice-daily administration is required, patient adherence will be vital to achieve the outcomes observed in PLATO.

6. Mega J, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374:29–38.

The ATLAS ACS-TIMI 46 trial was a randomized, double-blind, phase 2 dose-escalation study of rivaroxaban versus placebo in 3491 patients initially admitted with high-risk STEMI or NSTE ACS and then stabilized for 1–7 days before enrollment. Patients were then randomized to either rivaroxaban in total daily doses of 5–40 mg (administered in single or divided twice-daily doses) or placebo for 6 months. Patients with creatinine clearance less than 30 mL/minute were excluded, as were patients requiring treatment with warfarin. Rivaroxaban was added to low-dose aspirin therapy (75–100 mg daily), and patients were stratified for nonrandomized clopidogrel use (stratum 1 were patients not receiving a thienopyridine; stratum 2 were patients who received a thienopyridine). The primary end point was clinically significant bleeding, defined as TIMI major, TIMI minor, or bleeding requiring medical attention. The primary efficacy end point was a composite of death, MI, stroke, or recurrent ischemia requiring revascularization; the secondary efficacy end point was a composite of death, MI, or stroke.

About one-half of the patients enrolled (52%) were hospitalized with STEMI, whereas 31% had NSTE MI and 17% had unstable angina. There was a dose-dependent increase in clinically significant bleeding in rivaroxaban-treated patients compared with placebo (HR = 2.21, 95% CI, 1.25–3.91 for 5 mg; HR = 3.35, 95% CI, 2.31–4.87 for 10 mg; HR = 3.60, 95% CI, 2.32–5.58 for 15 mg; and HR = 5.06, 95% CI, 3.45–7.42 for 20 mg, $p<0.0001$). A trend toward a reduction in the rate of the primary efficacy end point, death, MI, stroke, or recurrent ischemia was observed with rivaroxaban (5.6% vs. 7.0%, HR = 0.79, 95% CI, 0.60–1.05, $p=0.10$). The secondary efficacy end point of 6-month rate of death, MI, or stroke was lower in rivaroxaban-treated patients than in placebo (3.9% vs. 5.5%, HR = 0.69, 95% CI, 0.50–0.96, $p=0.027$). This benefit appeared confined to the stratum of patients who did not receive concomitant (nonrandomized) thienopyridine, but the interaction term between stratum 1 and stratum 2 was not significant ($p=0.19$). No difference was observed in the rate of clinically significant bleeding or in the efficacy outcomes between once-daily and twice-daily rivaroxaban dosing. Nor was any evidence of liver injury observed. Because of the increased bleeding risk observed with higher doses and the similar efficacy observed with lower doses, the ATLAS ACS TIMI-51 trial is now studying two rivaroxaban doses, 2.5 mg twice daily and 5 mg twice daily.

7. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non–ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009;119:1873–82.

This landmark study created a scoring system for estimating bleeding risk in patients with NSTE ACS. The risk score was developed from a derivation cohort of 71,277 patients enrolled in CRUSADE between February 15, 2003, and December 31, 2006. The independent predictors of CRUSADE major bleeding are described in Table 1-5. The validation cohort consisted of 17,857 different CRUSADE patients enrolled at the same time. The score definitions were divided into quintiles of very low risk, low risk, moderate risk, high risk, and very high risk. In this registry, like many others, bleeding rates for even low risk were higher than those reported in clinical trials because of the more conservative patient selection, with respect to bleeding risk, in clinical trials. For example, the CRUSADE registry has a higher percentage of women and has more than 25% of patients with creatinine clearance less than 45 mL/minute. The in-hospital mortality in this CRUSADE population was 2.7%, which is 1.5 times the 9-day death rate in the OASIS-5 trial, twice as high as the 30-day mortality reported in the ACUITY trial, and 3 times as high as the 96-hour mortality rate reported in Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS), the most recent NSTE ACS trial. The risk of major bleeding was higher across quintiles in patients receiving two or more versus less than two antithrombotics, as well as those receiving an invasive versus conservative approach. Whether more careful selection of treatment strategies for those at high and very high risk can reduce bleeding risk requires a prospective clinical trial. Work is under way on validating this tool in another registry, the NCDR-ACTION GWTG Registry.

8. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brand JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553–60.

This landmark substudy of 1477 patients who provided a DNA sample in the TRITON-TIMI 38 trial is often cited as supporting the pharmacogenetic basis for differing patient responses to clopidogrel. Clopidogrel is a prodrug converted to an active metabolite in a two-step process involving CYP1A2, CYP2C19, CYP2B6, CYP3A5, and CYP2C9. This trial compared the differences in pharmacokinetics, antiplatelet response (pharmacodynamics), and clinical outcomes of clopidogrel between patients with at least one reduced-function allele for the genes encoding

these enzymes and noncarriers. Antiplatelet response was measured using light transmission aggregometry in response to 20 micromoles of ADP.

In the 152 patients in the pharmacokinetic study, the AUC of the active metabolite of clopidogrel was significantly reduced in patients who carried at least one reduced-function allele for CYP2C19 (−32.2%, p<0.001) and in those with at least one reduced-function allele for CYP2B6 (−15.7%, p=0.03). Of the 152 patients included in the pharmacodynamic study, maximal platelet response was reduced in patients with at least one reduced-function allele for CYP2C19 (−9%, p<0.001) and in those with at least one reduced-function allele for CYP2B6 (−5.7%, p=0.012); platelet response was increased in patients with at least one reduced-function allele for CYP3A5 (+7.5%, p=0.012) compared with noncarriers. The rates of both the 15-month primary efficacy outcome (death from CV causes, MI, or nonfatal stroke) (12.1% vs. 8.0%, HR = 1.53, 95% CI, 1.07–2.19) and stent thrombosis (2.6% vs. 0.8%, HR = 3.09, 95% CI, 1.19–8.00) were higher in carriers of at least one reduced-function *CYP2C19* allele compared with noncarriers, whereas bleeding rates were not statistically different (major or minor bleeding 2.9% vs. 3.0%, p=0.98). Major bleeding rates were not reported separately. The *CYP2C19*2* allele was present in 95% of reduced-function carriers.

In a separately published report regarding the identical substudy of patients randomized to prasugrel (Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553–60.), no relationship was found between the presence of at least one reduced-function allele for the *CYP* genes tested and prasugrel's pharmacokinetics, antiplatelet effect, or clinical outcomes (composite primary efficacy outcome, major or minor bleeding; or individual components of CV death, MI, and nonfatal stroke). With reduced-function carriers making up about 30% of the population, this finding has clinical relevance. The FDA and drug manufacturer are evaluating the possibility of recommending pharmacogenetic testing in the selection of appropriate clopidogrel candidates.

9. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

The TRITON-TIMI 38 trial compared the incidence of the primary composite end point of CV death, MI, and stroke, as well as TIMI major or minor non-CABG bleeding events, in patients with either NSTE ACS or STEMI undergoing PCI. Patients were randomized to either prasugrel 60-mg loading dose followed by 10 mg once daily orally or clopidogrel 300-mg loading dose followed by 75 mg daily orally for 15 months. Detailed outcomes of the trial, represented in Figure 1-4 and Figure 1-5, show the superiority of prasugrel in reducing ischemic events at 15 months while increasing TIMI major bleeding events in the overall cohort. The rate of life-threatening bleeding (defined as TIMI major bleeding that is fatal, that leads to hypotension requiring treatment with intravenous inotropic agents, that requires surgical intervention for continuing bleeding, that necessitates transfusion of 4 or more units of whole blood or packed red blood cells during a 48-hour period, or that is a symptomatic intracranial hemorrhage) was 1.4% for prasugrel versus 0.9% for clopidogrel (p=0.01). Fatal bleeding was 0.4% for prasugrel versus 0.1% for clopidogrel (p=0.002). In the overall cohort, the rate of nonfatal MI was significantly reduced with prasugrel compared with clopidogrel (7.3% vs. 9.5%, HR = 0.76, 95% CI, 0.67–0.85), but there was no difference in total mortality, CV death, or stroke.

In the subgroups of patients with either STEMI or DM, prasugrel significantly lowered the rate of ischemic events without increased risk of major bleeding (Figure 1-4 and Figure 1-5). In the subgroup of patients with NSTE MI, the rate of ischemic events was lower with prasugrel than with clopidogrel. Bleeding rates have not yet been reported for this subgroup. This study has been criticized because the 300-mg loading dose of clopidogrel has been found to have a slightly longer onset of antiplatelet action than the 600-mg dose. However, a separate trial has shown that prasugrel 60 mg has significantly greater antiplatelet activity than 600 mg of clopidogrel. In TRITON-TIMI 38, prasugrel reduced the rates of CV death (4.27% vs. 5.24%, HR = 0.81, 95% CI, 0.70–0.95), stent thrombosis (33% vs. 0.67%, HR = 0.49, 95% CI, 0.29–0.82), and target-vessel revascularization (0.54% vs. 0.83%, HR = 0.66, 95% CI, 0.43–0.99) without increasing TIMI major non-CABG bleeding at day 3 (0.74% vs. 0.61%, HR = 1.22, 95% CI, 0.81–1.84), suggesting that this earlier antiplatelet action of prasugrel is of clinical importance. Indeed, some have suggested that prasugrel be selected early and then patients changed to clopidogrel as an outpatient post-PCI to avoid increased risk of major bleeding later.

Prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack because in that subgroup, the rate of NACE was significantly higher with prasugrel than with clopidogrel (HR = 1.54, 95% CI, 1.02–2.32), and a history of stroke or transient ischemic attack was a risk factor for bleeding. Other potential patient groups warranting caution because of a higher bleeding risk with prasugrel compared with clopidogrel are those 75 years or older, patients weighing less than 60 kg, and those undergoing CABG surgery. It is recommended that prasugrel be discontinued at least 7 days before CABG surgery, whereas 5 days is recommended for clopidogrel. Bleeding related to CABG was more than 3-fold higher in patients receiving prasugrel compared with clopidogrel (11.3% vs. 3.6%, p=0.002). Product labeling indicates that prasugrel should not be administered in patients expected to undergo CABG; therefore, clinicians are likely to withhold prasugrel until coronary anatomy is known just before PCI and not administer prasugrel in the emergency department.

Prasugrel's label suggests that patients older than 75 years not receive prasugrel unless they are in a subgroup of patients likely to benefit (e.g., those with DM or prior MI). Fatal hemorrhage was 10-fold higher in prasugrel-treated patients older than 75 than in clopidogrel-treated patients (1.01% vs. 0.11%, p value not specified), whereas

the incidence of the primary efficacy end point was similar (16% vs. 17%, p=0.53).

In patients weighing less than 60 kg, exposure to clopidogrel's active metabolite is increased compared with patients weighing 85 kg (49% for C_{max} and 45% for AUC). For TIMI, non-CABG major bleeding was increased more than 3-fold in prasugrel-treated patients weighing less than 60 kg than in those weighing 60 kg or more (HR = 3.05, 95% CI, 2.01–4.62). Body weight was a significant predictor of bleeding in multivariate analysis as well (HR = 2.83, p<0.001); however, body weight was not a significant predictor of efficacy in a multivariate analysis. Therefore, product labeling recommends a lower maintenance dose of prasugrel (5 mg once daily) for patients weighing less than 60 kg. Simulation pharmacokinetic data show that such a dose reduction would result in prasugrel active metabolite concentrations similar to those in the lower two quartiles of patients receiving a 10-mg dose weighing and more than 60 kg. Although no clinical trial outcomes data exist for patients randomized to a 5-mg dose, a trial is under way.