Antithrombotic Therapies in Acute Coronary Syndrome

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LEARNING OBJECTIVES

1. Distinguish the types of myocardial infarction that can occur in critically ill patients.
2. Evaluate the acute use of antiplatelet and anticoagulant therapies for patients with ischemic heart disease.
3. Develop appropriate management of chronic antithrombotic pharmacotherapies for ischemic heart disease in critically ill patients.
4. Demonstrate appropriate management of antithrombotic toxicities and adverse effects in patients with ischemic heart disease.

ABBREVIATIONS IN THIS CHAPTER

ACS	Acute coronary syndrome
BMS	Bare metal stent
CABG	Coronary artery bypass grafting
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
GPI	Glycoprotein IIb/IIIa inhibitor
HIT	Heparin-induced thrombocytopenia
NSTE ACS	Non−ST-segment elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
UA	Unstable angina
UFH	Unfractionated heparin

Table of other common abbreviations.

INTRODUCTION

Acute coronary syndrome (ACS) continues to contribute to the significant morbidity and mortality related to cardiac disease, which remains the leading cause of death in the United States. About 15.5 million Americans have coronary heart disease with over 900,000 coronary events each year, which accrue over $200 billion in direct and indirect costs (Mozaffarian 2016). Endogenous thrombosis pathways, including activation of the clotting cascade and platelet aggregation, are a key component of the pathophysiology of ACS. Specifically, platelets serve critical roles as "first responders" to injured vascular endothelium by interacting with subendothelial constituents, leading to platelet adhesion, activation, and aggregation and resulting in platelet-mediated thrombosis. Platelet activation also promotes inflammatory cytokine release as well as clotting cascade activation, which often initiates and accelerates hemodynamically significant clot formation within the coronary lumen. Therefore, optimal inhibition of thrombosis is paramount in the treatment of ACS. Acute coronary syndrome is recognized as a spectrum of disease, including unstable angina (UA), non−ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), but appropriate inhibition of thrombosis is indicated in all phases of ACS.

Recognizing ACS events in critically ill patients is complicated for many different reasons. These may include ECG monitoring, which is less sensitive and specific; lack of patient responsiveness

to ischemic chest pain as the result of continuous analgesia or altered mental status; and complications of myocardial infarction (MI), such as arrhythmia or hypotension, which are relatively nonspecific in a critically ill patient with a broad differential diagnosis (Klouche 2014).

Objective markers of myocardial necrosis, such as cardiac biomarkers, are also difficult to interpret in critically ill patients. Plasma troponin concentration, a standard for the diagnosis of MI, is unreliable in critically ill patients because of the assay's extreme sensitivity in distinguishing myocardial ischemia caused by coronary thrombosis from a wide range of pathologies. More than 60% of critically ill patients may have a detectable plasma troponin concentration (Hamilton 2012). Transient cardiac biomarkers in critically ill patients can greatly confuse the specific diagnosis and cause harm from misapplied therapies. For example, one group of investigators identified that of 171 patients admitted to an ICU, 42.1% had elevated troponin I concentrations, but only 22.2% of all patients had an MI (Lim 2006). To this end, key stakeholders from leading cardiovascular societies in the United States and worldwide have developed a universal definition of MI to delineate the specific causes of myocardial ischemia, which is now in its third iteration (Table 1-1).

A critically ill patient population appears likely to have a high prevalence of type 2 infarcts, or infarcts related to a disruption between myocardial oxygen supply and demand, usually because of concomitant illness or medical stress (Ammann 2003; Lee 2015). Antithrombotic therapy is unlikely to be of significant value in these patients, and care to ensure the appropriate source of ischemia is paramount among the medical professionals caring for the patient. The gold standard diagnosis of myocardial ischemia related to coronary thrombosis remains cardiac catheterization. However, catheterization may not be feasible in critically ill patients for reasons such as instability and bleeding risk, which makes the actual diagnosis significantly more difficult to ascertain. Identifying the source of myocardial ischemia before applying treatment, likely in consultation with a cardiologist, is vital to achieving optimal outcomes.

TREATMENT STRATEGIES FOR ACS IN CRITICALLY ILL PATIENTS

Patients with ACS of suspected coronary thrombotic origin need urgent evaluation and management of their ischemia. In particular, patients with STEMI need immediate reperfusion. Earlier reperfusion has been associated with improved clinical outcomes, including surrogate markers of myocardial perfusion, reinfarction, and mortality; early reperfusion is recommended in the current guidelines (Fibrinolytic Therapy Trialists' (FTT) Collaborative Group 1994; O'Gara 2013). Various modalities to treat ACS have evolved, prioritizing early and effective reperfusion. Common reperfusion strategies include fibrinolysis, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) surgery. These are termed an *early invasive strategy* in the guidelines. If an early invasive strategy is not pursued, an ischemia-guided strategy is indicated (Amsterdam 2014).

The specific interaction between the reperfusion strategy and the optimal antithrombotic therapy depends on the overarching treatment strategy used and the diagnosis of STEMI compared with non–ST-segment elevation acute coronary syndrome (NSTE ACS) (Figure 1-1). Treatment may be different depending whether the patient is in the pre-, peri-, or post-procedural stage of care. When the time of initial presentation to the time of revascularization is very short (e.g., primary PCI for STEMI), there is little to no distinction between pre- and peri-procedural management. However, other scenarios may have distinct periods of pre- versus peri-procedural management (e.g., PCI for NSTE ACS).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:
- General treatments and approaches to the management of acute coronary syndrome
- Coronary and cardiac anatomy and physiology
- Pharmacologic properties of various anticoagulant and antiplatelet therapies

Table of common laboratory reference values.

ADDITIONAL READINGS

- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.
- Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.

Table 1-1. Universal Definition of MI and Antithrombotic Therapies

Type	Description	Considerations for Antithrombotic Therapies
1	**Spontaneous MI:** Related to coronary plaque rupture, ulceration, or erosion leading to thrombus formation and subtotal or total coronary occlusion	Indicated by guidelines
2	**Ischemic imbalance:** Myocardial necrosis from a condition other than coronary artery disease contributed to an imbalance between myocardial oxygen supply and demand	Not indicated and may be harmful in some scenarios
3	**Sudden death:** Patients with ECG changes and symptoms of myocardial ischemia but unable to confirm biomarkers because the patient died	N/A
4	**Procedural infarction:** Related to thrombosis induced by PCI (type 4a) and stent thrombosis (type 4b)	Possible benefit
5	**Cardiac surgery infarction:** Infarction related to cardiac bypass grafting surgery	Possible benefit-risk from surgical bleeding

MI = myocardial infarction; N/A = not applicable; PCI = percutaneous coronary intervention.

Information from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
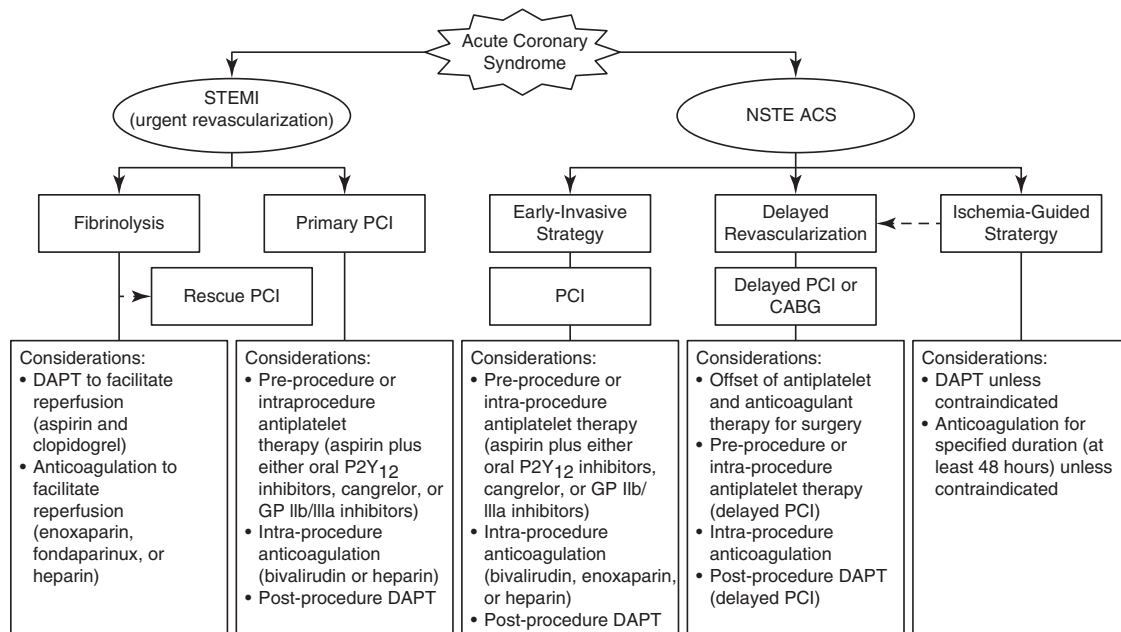

Figure 1-1. Antiplatelet and antithrombotic therapy for acute coronary syndrome. This figure depicts general recommendations for the two major strata of acute coronary syndrome regarding antiplatelet and antithrombotic therapy. Usefulness and duration of antiplatelet therapy depend greatly on the modality of reperfusion and whether an ischemia-guided strategy is chosen.

CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; NSTE ACS = non−ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Information from: Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228; and O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Fibrinolysis

Fibrinolysis was the initial reperfusion strategy for STEMI, which consisted of administering a fibrinolytic agent to reestablish coronary perfusion. Its benefits in reducing morbidity and mortality in patients with STEMI when given within 12 hours of symptom onset are well established (Fibrinolytic Therapy Trialists' (FTT) Collaborative Group 1994; Pinto 2011). Until the advent of PCI, fibrinolysis was the most common approach to early reperfusion for patients with STEMI. Percutaneous coronary intervention is superior to fibrinolysis if reperfusion can be attained within 120 minutes from first medical contact (Huynh 2009; Keeley 2003; Pinto 2011). Thus, fibrinolysis is now generally reserved for patients with STEMI presenting to hospitals without PCI capabilities who cannot be transferred to another PCI-capable hospital within 120 minutes from first medical contact. These patients are often transported to a PCI-capable facility after fibrinolysis to undergo angiography for evaluation of reperfusion success and evaluation of the coronary anatomy, generally before hospital discharge. After fibrinolysis, if patients have cardiogenic shock or acute heart failure or if reperfusion has failed (lack of major ST resolution and absence of reperfusion arrhythmias), guidelines recommend urgent transfer for rescue PCI (O'Gara 2013). Absolute and relative contraindications to fibrinolysis in MI are listed in Table 1-2. Critically ill patients may be more likely than most populations to have these complicating issues.

Antithrombotic therapy plays an important role in facilitating and sustaining reperfusion in patients receiving fibrinolytic therapy for STEMI. The guidelines recommend unfractionated heparin (UFH), enoxaparin, or fondaparinux (O'Gara 2013). Compared with UFH, enoxaparin decreases the recurrence of MI and urgent revascularization, but possibly at the cost of increased nonfatal major bleeding (Antman 1999). Although the net clinical benefit favors the use of enoxaparin, individual patients should be considered to weigh the risks of bleeding versus the ischemic benefits. Although the guidelines prefer no particular anticoagulant, fondaparinux should be used with caution in this setting. Despite data showing improved outcomes in patients receiving fibrinolysis alone, patients who subsequently undergo PCI may have worse procedural outcomes and are at risk of catheter thrombosis if not given another anticoagulant at the time of PCI (see section on peri-procedural anticoagulation that follows) (Yusuf 2006).

Dual antiplatelet therapy (DAPT) is also indicated for patients receiving fibrinolytic therapy for STEMI. Aspirin reduced vascular mortality in combination with streptokinase in the ISIS-2 trial (ISIS-2 Collaborative Group 1988). In CLARITY, use of clopidogrel in addition to aspirin and standard fibrinolytic therapy was associated with greater arterial patency and reduced 30-day adverse cardiovascular outcomes compared with placebo. In addition, 30-day mortality was reduced with DAPT (Sabatine 2005). No data exist with newer $P2Y_{12}$ inhibitors for fibrinolytic therapy. Therefore, the choice of $P2Y_{12}$ inhibitor for fibrinolysis should be limited to clopidogrel at a loading dose of 300 mg, followed by 75 mg daily; patients older than 75 should receive 75 mg daily only because of their exclusion in CLARITY and concern for greater risk of bleeding.

Primary PCI

Having shown superiority to fibrinolysis in achieving arterial patency and mortality, PCI is now the preferred modality for the treatment of STEMI, with a goal of achieving coronary reperfusion within 90 minutes of institutional presentation (Keeley 2003; O'Gara 2013). Percutaneous coronary intervention techniques have evolved over the past 2 decades, starting with balloon angioplasty alone, progressing to bare metal stents (BMS), and now in the current era of drug-eluting stents (DES). The choice of using BMS versus DES often depends on various interventional factors and the ability to continue prolonged DAPT. However, DES are generally considered superior because of their reduced risk of in-stent restenosis. Another significant advancement in cardiac catheterization is the choice of access site. Traditionally, the coronary vessels have been accessed by the femoral artery because of ease of access. However, radial artery access has gained popularity because of the lower and less consequential risks associated with bleeding episodes, given that the radial artery is more compressible and bleeding is more easily attenuated. In the United States, adoption of radial artery access has increased from 2% in 2008 to 16% in 2012 (Feldman 2013). A radial approach decreases not only major bleeding but also mortality (Valgimigli 2015b; Ferrante 2016)). This has important implications because it affects the interpretation of bleeding outcomes when comparing various antithrombotic regimens in studies of patients undergoing PCI.

Pre-procedure

Pre-procedural antithrombotic therapy is largely used with the goals of successful clot stabilization and facilitation of intra-procedural success. Aspirin therapy (81–325 mg) is the recommended initial treatment for all phases of ACS, including STEMI, as well as before cardiac catheterization (Amsterdam 2014). This provides a baseline level of platelet inhibition and generally has been included as part of PCI procedures since their inception. In critically ill patients, non−enteric-coated aspirin products, ideally crushed, are recommended either orally or through feeding tubes because of their superior onset of action. If oral access is not available, aspirin suppositories can be considered, though they are less preferable, given the significant delay (up to 4 hours) in onset of action compared with crushed oral dosage forms. Using pre-procedural $P2Y_{12}$ inhibition to more completely inhibit platelet-driven thrombosis is controversial. Although this "preloading" is generally thought to facilitate PCI efficacy and is guideline recommended, the superiority of earlier $P2Y_{12}$ inhibition has

Table 1-2. Absolute and Relative Contraindications to Fibrinolysis in STEMI

Absolute Contraindications	Time Interval	Modifiable?
Prior intracerebral hemorrhage	Any	No
Known structural cerebral vascular lesion	Any	No
Known malignant intracranial neoplasm	Any	No
Prior ischemic stroke	Previous 3 mo	No
Suspected aortic dissection	N/A	Can be ruled out with ED imaging studies
Active bleeding or bleeding diathesis	N/A	Possibly
Significant closed-head or facial trauma	Previous 3 mo	No
Intracranial or intraspinal surgery	Previous 2 mo	No
Prior receipt of streptokinase	Previous 6 mo[a]	No
Relative Contraindications	**Time Interval**	**Modifiable?**
History of chronic, severe, poorly controlled hypertension	Any	Yes
Hypertension on presentation (SBP > 180 mm Hg or DBP > 110 mm Hg)	N/A	Yes
Dementia	Any	No
Known other intracranial pathology not covered in absolute contraindications	Any	No
Traumatic or prolonged (> 10 min) CPR	N/A	No
Major surgery	Previous 3 wk	No
Recent internal bleeding	Previous 2–4 wk	No
Noncompressible vascular punctures	N/A	No
Pregnancy	N/A	No
Active peptic ulcer	N/A	No
Oral anticoagulant therapy at presentation	N/A	Possibly

[a]With planned readministration of streptokinase.

CPR = cardiopulmonary resuscitation; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Information from: O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.

not been conclusively proven by a well-designed trial, even with use of a faster-acting oral $P2Y_{12}$ inhibitor. Cangrelor, an intravenous $P2Y_{12}$ inhibitor with rapid onset and a significantly shortened half-life, is an attractive alternative to oral agents in the pre-procedural STEMI setting. Unfortunately, all evidence to date for cangrelor has focused on the intra- and post-procedural settings. In addition, recovery of platelet function after receiving oral $P2Y_{12}$ inhibitor therapy occurs over a minimum of several days, regardless of drug choice. This presents challenges if the patient requires urgent surgical revascularization because performing surgery under the exposure of these agents increases surgical complications.

However, patients with STEMI rarely (less than 5% of cases) undergo surgical revascularization (Gu 2010). Gastric access is required for $P2Y_{12}$ inhibitors; no experience with alternative dosage forms exists, though crushed dosage forms appear to confer faster pharmacodynamic onset, leading to reduced platelet reactivity compared with whole tablets as soon as 30 minutes post-dose with prasugrel (Rollini 2016).

Patients with STEMI undergoing primary PCI also benefit from anticoagulant therapy, though given the very short goal interval between presentation and coronary reperfusion, most of these therapies are relegated to the intra-procedural setting. However, systems of care may be developed to

transition some intra-procedural therapies to be given in the pre-procedural setting so that the catheterization team can focus on site access and coronary reperfusion.

Intra-procedure

Almost all patients with STEMI (more than 95%) undergo PCI for rapid revascularization (Gogo 2007; Gu 2010). Introducing a catheter into the coronary arteries can be highly thrombogenic and requires aggressive adjunctive antithrombotic treatment. As such, drug selection, dosing, and routes of administration can vary considerably compared with those

in patients with NSTE ACS receiving anticoagulation either while waiting for PCI or while receiving ischemia-guided therapy only (Table 1-3).

Anticoagulant therapy for intra-procedural cardiac catheterization has evolved considerably in the past 2 decades. Historically, UFH was the agent used in conjunction with glycoprotein IIb/IIIa inhibitors (GPIs); it typically has been given as an intravenous bolus with potential repeat intravenous bolus doses to achieve target activated clotting time (ACT) goals. However, the introduction of bivalirudin has shifted this paradigm, with much controversy over which agent is better

Table 1-3. Pharmacologic Properties and Dosing of Anticoagulants Used in ACS

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Mechanism of Action	AT-mediated inhibition of factors II and X	AT-mediated inhibition of factors X > II	AT-mediated inhibition of factor X	Direct thrombin (II) inhibitor
Dosing	Fibrinolysis, NSTE ACS, or ischemia-guided therapy: • 60 unit/kg bolus (max 4000 units) + 12 units/kg/hr infusion (initial max 1000 units/hr), titrated to therapeutic aPTT for 48 hr or until revascularization PCI with planned GPI: • 50−70 units/kg IV bolus to achieve therapeutic ACT PCI without planned GPI: • 70−100 units/kg IV bolus to achieve therapeutic ACT	Fibrinolysis: • ≤ 75 yr: 30 mg IV bolus, then 15 min later 1 mg/kg SC q12hr (max 100 mg for first two doses, give first dose with initial IV dose) • >75 yr: No bolus, 0.75 mg/kg SC q12 hr (max 75 mg for first two doses) • CrCl < 30 mL/min/1.73 m^2: 30 mg IV bolus (omit if > 75 yr) and 1 mg/kg SC q24hr (give first dose with initial IV dose with max of 100 mg) • Duration is for index hospitalization up to 8 days, or until revascularization NSTE ACS/ischemia-guided therapy: 1 mg/kg SC q12hr for duration of hospitalization or until revascularization Primary PCI: • 0.5−0.75 mg/kg IV bolus if no anticoagulation previously 0.3 mg/kg IV if last SC dose was > 8 hr before PCI, or only one SC dose given	Fibrinolysis: • 2.5 mg IV x 1, then 2.5 mg SC daily starting the next day for index hospitalization up to 8 days, or until revascularization NSTE ACS/ischemia-guided therapy: • 2.5 mg SC daily for duration of hospitalization or until revascularization PCI: • Not recommended without additional anticoagulant with anti-II activity	ACS: • 0.15−2 mg/kg/hr infusion, titrated to aPTT goal PCI: • 0.75 mg/kg IV bolus + 1.75 mg/kg/hr infusion
Monitoring	aPTT, anti-Xa, and/or ACT (200−250 s during PCI with GPI or 250−300 s without GPI), Hgb, Hct, Plt	Renal function, Hgb, Hct, Plt, anti-Xa (as indicated)	Renal function, Hgb, Hct	PTT and/or ACT as indicated, renal function, Hgb, Hct
Onset	Immediate	IV: Immediate SC: 2 hr	IV: Immediate SC: 2 hr	Immediate
Duration	1−2 hr	IV: 6 hr SC: 12 hr (longer with renal dysfunction)	17−21 hr (longer with renal dysfunction)	1−3 hr based on renal function

ACS = acute coronary syndrome; ACT = activated clotting time; aPTT = activated PTT; anti-Xa = anti-factor Xa; AT = antithrombin; GPI = glycoprotein IIb/IIIa inhibitor; IV = intravenous(ly); NSTE ACS = non−ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; q = every; SC = subcutaneous(ly); UFH = unfractionated heparin.

Table 1-4. Landmark Studies Comparing Bivalirudin with UFH for PCI

Study (yr)	Pertinent Inclusion/Exclusion Criteria	Intervention/Methods	End Points	Pertinent Baseline Characteristics	Outcomes

ACUITY (2006)	Incl.: NSTE ACS Excl: STEMI	Three arms: 1) UFH or enoxaparin + GPI 2) Bivalirudin + GPI 3) Bivalirudin alone ± bailout GPIIb/IIIa	• Composite of death, MI, unplanned revascularization
			• Major bleeding
			• Net benefit (composite + major bleeding)
				n=13,189
				NSTEMI 59%,
				UA 41%
				PCI 55%
				ASA 98%,
				  clopidogrel 63%
				Radial access:
				Arm 1: 47% UFH,
				  47% enoxaparin
					• Arm 2 vs. 1: noninferior in composite, major bleeding, and net clinical outcome
					• Arm 3 vs. 1: noninferior in composite; superior in bleeding (3.0% vs. 5.7%, RR 0.53, p<0.001) and net clinical outcome (10.1% vs. 11.7%, RR 0.86, p=0.015)

HORIZONS-AMI (2008)	Incl: STEMI Excl: NSTE ACS	Two arms: 1) UFH + universal GPI 2) Bivalirudin + provisional GPI	• Major bleeding • Net adverse clinical events (major bleeding or MACE)	n=3602 GPI use in 7.2% of bivalirudin arm, clopidogrel 98%	• Major bleeding: bivalirudin 4.9% vs. 8.3%, RR 0.60 (p<0.002) • Net events: 9.2% vs. 12.1%, RR 0.76 (p=0.005) • All-cause mortality: 2.1% vs. 3.1%, RR 0.66 (p=0.047) • Acute stent thrombosis: 1.3% vs. 0.3%, RR 4.3 (p<0.001)
ISAR-REACT 4 (2011)	Incl: NSTEMI with definite planned PCI Excl: STEMI, UA	Two arms: 1) UFH + abciximab 2) Bivalirudin	• Composite of death, large recurrent MI, urgent TVR, major 30-day bleeding • Major bleeding	n=1721 88% DES 99% femoral access	• No difference in composite outcome • Major bleeding UFH 4.6% vs. 2.6%, RR 1.84 (p=0.02)

EUROMAX (2013)	Incl: STEMI Excl: NSTE ACS	Two arms: 1) Bivalirudin + provisional GPI+ post PCI bivalirudin x 4 hr 2) UFH/ enoxaparin + provisional GPI	• Composite: death or major non-CABG bleeding
			• Net events (MACE + non-CABG bleeding)
				n=2218
				Clopidogrel 40%,
				  prasugrel 30%,
				  ticagrelor 30%
				UFH 90%,
				  enoxaparin 8.5%
				GPI use: 11.5% vs. 69%
				Radial access: 46%
					• Composite: bivalirudin 5.1% vs. 8.5%, RR 0.60 (p=0.001)
					• MACE: 6.0% vs. 5.5%, RR 1.09 (p=0.64)
					• Net events: 6.6% vs. 9.2%, RR 0.72 (p=0.02)
					• Major bleeding: 2.6% vs. 6.0%, RR 0.43 (p<0.001)
					• Acute stent thrombosis: 1.1% vs. 0.2%, RR 6.11 (p=0.007)

HEAT-PPCI (2014)	Incl: STEMI	Two arms: 1) Bivalirudin (provisional GPI allowed) 2) UFH (provisional GPI allowed)	• MACE (death, CVA, reinfarction, unplanned revascularization)
			• Major bleeding
				n=1812
				Clopidogrel 11%,
				  prasugrel 28%,
				  ticagrelor 62%
				Radial access 80%
				GPI: UFH group 15% vs.
				  bivalirudin group 13%
					• MACE: Bivalirudin 8.7% vs. 5.7%, RR 1.54 (p=0.01)
					• Major bleeding: 3.5% vs. 3.1% (p=0.59)

BRAVE-4 (2014)	Incl: STEMI	Two arms: 1) Bivalirudin + prasugrel (provisional GPI allowed) 2) UFH + clopidogrel (provisional GPI allowed)	• Composite: death, MI, unplanned revascularization, stent thrombosis, stroke, major bleeding	Trial stopped early for low recruitment n=548 GPI use: Bivalirudin 3.0 % vs. UFH 6.1% Femoral access: 99%	• Composite: Bivalirudin 15.6% vs. 14.5% (p=0.680) • Bleeding: 14.1% vs. 12.0% (p=0.543)

(Continued)

Table 1-4. (Continued)

Study (yr)	Pertinent Inclusion/ Exclusion Criteria	Intervention/ Methods	End Points	Pertinent Baseline Characteristics	Outcomes
MATRIX (2015)	Incl: STEMI or NSTEMI; PCI candidate	Two arms: 1) Bivalirudin + provisional GPI (group subsequently randomized to receive post PCI bivalirudin x 4 hr vs. placebo) 2) UFH + provisional GPI	• MACE: Composite of all-cause death, MI, stroke up to 30 days • Net events: Major non-CABG bleeding + MACE up to 30 days • Post-PCI infusion outcome: Composite of urgent TVR, definite stent thrombosis, or net adverse clinical events up to 30 days	n=7213 Clopidogrel 46%, prasugrel 24%, ticagrelor 13% GPI use: 4.6% vs. 26% Radial access: 50%	• MACE: bivalirudin 10.3% vs. 10.9% (p=0.44, note: UFH + *planned* GPI rate was 8.1%) • Net events: 11.2% vs. 12.4% (p=0.12, note: UFH + *planned* GPI rate was 10.6%) • Post PCI infusion: infusion 11.0% vs. no infusion 11.9% (p=0.34) • Major bleeding: 1.4% vs. 2.5%, RR 0.55 (p<0.001) • Death: 1.7% vs. 2.3%, RR 0.71 (p=0.04)
BRIGHT (2015)	Incl: STEMI or NSTEMI Excl: Prior anticoag	Three arms: 1) Bivalirudin + post PCI infusion (30 min – 4 hr) 2) UFH 3) UFH + tirofiban	• Net events: MACE + or any bleeding • MACE • Any bleeding	n=2194 STEMI 90% Clopidogrel 100% Radial access 78.5%	• Arm 1 vs. 2: 8.8% vs. 13.2%, RR 0.67 (p=0.008) • Arm 1 vs. 3: 8.8% vs. 17.0%, RR 0.52 (p<0.001) • No differences in MACE • Bleeding: 4.1% vs. 7.5% vs. 12.3% (p<0.001)

CABG = coronary artery bypass grafting; DES = drug-eluting stent; UA = unstable angina.

(Table 1-4). Each agent has drug-specific characteristics that may influence its use. Although rare, heparin carries a risk of heparin-induced thrombocytopenia (HIT) in 0.1%−5% of patients. Bivalirudin has more consistent anticoagulant effects and, unlike UFH, can bind clot-bound thrombin, an important substrate for platelet activation and fibrin formation. Therefore, bivalirudin would be expected to inhibit a larger pool of thrombin compared to UFH. However, it requires a continuous infusion intra-procedurally, needs dose-adjustment for renal dysfunction, and is significantly more expensive than UFH.

Bivalirudin and UFH are two of the most extensively studied adjunctive anticoagulants for primary PCI. The HORIZONS-AMI study with bivalirudin established efficacy and safety in PCI therapy in patients with STEMI, which showed bivalirudin to be noninferior to UFH with respect to ischemic outcomes (despite an increase in acute stent thrombosis) while reducing major bleeding outcomes (Stone 2008). Because HORIZONS-AMI is almost a decade old, clinicians have questioned whether its results are still valid. Percutaneous coronary intervention treatments have rapidly evolved over the past 15 years, potentially affecting the study's applicability to current practices. Some important variables to consider when comparing studies include the types of stents used, radial versus femoral access, use of GPIs, and use, choice, and dosage of P2Y$_{12}$ inhibitors. Some recent studies using contemporary PCI practices have provided similar results to HORIZONS-AMI (see Table 1-3) (Kastrati 2011; Valgimigli 2015a; Steg 2013; Han 2015).

In contrast, other recent studies have challenged the superiority of bivalirudin over UFH, causing much debate. The HEAT-PPCI (n=1812) trial compared bivalirudin with UFH with provisional GPI use for either arm in patients with STEMI undergoing primary PCI (Shahzad 2014). Most patients received ticagrelor (62%) or prasugrel (28%), and 81% had a radial artery approach. The groups had similar GPI use (13% vs. 15%). The outcomes differed from previous studies in that ischemic events were more common with bivalirudin (8.7% vs. 5.7%, RR 1.54, p=0.01), and the incidence of major bleeding did not differ between the two groups, possibly because of the more stringent bleeding definition used in the trial. Although previous studies with bivalirudin in subsets of troponin-positive patients have trended toward worse outcomes compared with heparin plus GPI (Stone 2006; Kastrati 2011), this study defied the prevalent view that bivalirudin is superior in PCI. Possible reasons for the discordant results include low use of GPIs (possibly because of the high use of newer P2Y$_{12}$ inhibitors) and more access by the radial artery.

However, other contemporary studies with similar patient populations argue that bivalirudin continues to decrease bleeding (Steg 2013; Han 2015; Valgimigli 2015a). The BRAVE-4

compared bivalirudin plus prasugrel with UFH plus clopidogrel in patients with STEMI undergoing PCI. The study was terminated early because of slow recruitment (n=548 of planned 1240). All patients underwent femoral arterial access, and GPI use was low (3% vs. 6%). The study was unable to show differences in ischemic or bleeding outcomes, although it was underpowered. These newer data challenge the idea that bivalirudin improves patient outcomes. However, newer practices such as use of radial access and decreased GPI, as well as newer $P2Y_{12}$ inhibitor use may lead to outcomes with UFH to be more similar to those of bivalirudin and provide an overall more attractive and cost-effective treatment.

Other options for anticoagulation in the PCI setting include enoxaparin and fondaparinux. Enoxaparin dosing is different for patients with STEMI, who are generally taken emergently to the catheterization laboratory (see Table 1-3). Data describing this strategy used a high rate of radial artery access. Thus, the safety outcomes of enoxaparin in patients with STEMI receiving PCI with femoral artery access are less well known. Otherwise, considerations for enoxaparin are the same as previously described. Fondaparinux has also been compared with UFH in patients with STEMI, with no difference in overall outcomes (Yusuf 2006). However, there was an increase in guidewire catheter thrombosis, which led the STEMI guidelines to recommend against fondaparinux as a sole agent in PCI (O'Gara 2013).

Intra-procedural antiplatelet therapy is also important to ensure successful PCI outcomes. Historically, this has been accomplished rapidly and completely with the use of GPIs, which prevent platelet aggregation and significantly attenuate platelet-driven thrombosis (Table 1-5). Typical regimens

Table 1-5. Pharmacologic Properties of Antiplatelet Therapy Used for ACS

Agent	Mechanism of Action	Utility	Dosing	Dose Adjustments	Monitoring	Onset	Elimination Pathway	Recovery of Platelet Function
Aspirin	Inhibits Thromboxane A_2 production	Treatment of ACS (all phases) and secondary prevention; prevention of stent thrombosis	162−325 mg (acute); 81−325 mg (chronic)	None	Bleeding, gastric adverse effects, allergic reactions	~1−2 hr; 20 min if chewed	Hepatic conjugation; renal excretion Platelet turnover – irreversibly binds to platelets	~5 days
Clopidogrel	Thienopyridine $P2Y_{12}$ inhibitor – requires 2-step metabolism to active metabolite	Treatment of ACS (all phases) and secondary prevention; prevention of stent thrombosis	300−600 mg (acute); 75 mg daily (chronic)	None	Bleeding	~2 hr (600 mg) ~6 hr (300 mg) ~3−5 days (75 mg daily)	Platelet turnover – irreversibly binds to platelets	~5−7 days
Prasugrel	Thienopyridine $P2Y_{12}$ inhibitor – requires 1-step metabolism to active metabolite	Treatment of ACS associated with PCI, prevention of stent thrombosis	60 mg (acute); 10 mg daily (chronic)	Reduce to 5 mg daily if weight < 60 kg	Bleeding	~30 min	Platelet turnover – irreversibly binds to platelets	~5−10 days
Ticagrelor	$P2Y_{12}$ inhibitor	Treatment of ACS with or without PCI; prevention of stent thrombosis	180 mg (acute); 90 mg BID (chronic)	Avoid use in severe hepatic impairment	Bleeding, dyspnea, uric acid concentrations	~30 min	Hepatic by CYP3A4 (contraindicated with strong inhibitors/inducers); inhibits P-glycoprotein	~3−5 days

(Continued)

Table 1-5. (*Continued*)

Agent	Mechanism of Action	Utility	Dosing	Dose Adjustments	Monitoring	Onset	Elimination Pathway	Recovery of Platelet Function
Cangrelor	$P2Y_{12}$ inhibitor	Procedural antiplatelet therapy for PCI	PCI: 30 mcg/kg IV bolus, 4 mcg/kg/min infusion for at least 2 hr Bridge to surgery: 0.75 mcg/kg/min	None	Bleeding	2 min (bolus)	Plasma dephosphory lation	~1 hr
Eptifibatide	GPI	Procedural antiplatelet therapy for PCI	180 mcg/kg IV bolus (max 22.6 mg) x 2 for PCI, followed by 2 mcg/kg/min (max 15 mg/hr) infusion for 18-24 hr (operator discretion)	Reduce infusion to 1 mcg/kg/min if CrCl < 50 mL/min; contraindicated in ESRD	Bleeding, Plt	Immediate (bolus)	Primarily renal	~4−8 hr
Tirofiban	GPI	Procedural antiplatelet therapy for PCI	25 mcg/kg IV bolus followed by 0.15 mcg/kg/min for 18−24 hr (operator discretion)	Reduce to 0.075 mcg/kg/min if CrCl < 60 mL/min	Bleeding, Plt	Immediate (bolus)	Primary renal	~4−8 hr
Abciximab	GPI	Procedural antiplatelet therapy for PCI	0.25 mg/kg IV/IC bolus, followed by 0.125 mcg/kg/min (max 10 mcg/min) for 12 hr	None	Bleeding, Plt	Immediate (bolus)	Proteolytic cleavage	12−24 hr

BID = twice daily; ESRD = end-stage renal disease.

include an intravenous bolus at the time of PCI and a post-procedural course to prevent acute stent thrombosis and allow for oral $P2Y_{12}$ inhibitor onset. Recently, the advent of high-dose bivalirudin and more rapidly acting oral $P2Y_{12}$ inhibitors has largely supplanted the routine use of procedural GPI through improved safety indices. Today, much GPI use is therefore through so-called "bailout" (i.e., non-planned use), though this approach has not been prospectively evaluated. These uses are largely procedural phenomena such as slow-reflow of an occluded coronary artery (implying distal or microvascular occlusion), high-risk interventions, or large clot burden at the operator's discretion.

Continuous intravenous cangrelor during PCI offers an attractive alternative to pre-procedural (or later) $P2Y_{12}$ inhibitor preloading as a reversible and short-acting $P2Y_{12}$ inhibitor. In the CHAMPION-PHOENIX trial, intravenous cangrelor reduced a composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours compared with clopidogrel (4.7% vs. 5.9%, p=0.005), the benefit for which persisted up to 30 days post-procedure (Table 1-6) (Bhatt 2013). Cangrelor also reduced procedural thrombotic events, including stent thrombosis, compared with clopidogrel when both therapies were given at the time of PCI. Various bleeding indices were also increased with cangrelor relative to clopidogrel, some of which were statistically different. Of importance, intravenous cangrelor must be carefully transitioned to an oral $P2Y_{12}$ inhibitor. There is a competitive pharmacodynamic interaction such that thienopyridine $P2Y_{12}$ inhibitors must be given after cangrelor is discontinued and no sooner because the active metabolite generated by these compounds is unstable and may be metabolized before the offset of cangrelor (Steinhubl 2008). Ticagrelor may be used irrespective of

Table 1-6. Landmark Studies of Antiplatelet Agents in ACS with PCI

Study (Year)	Pertinent Inclusion/ Exclusion Criteria	Intervention/ Methods	End Points	Pertinent Baseline Characteristics	Outcomes
CURE (2001)	Incl: NSTE ACS Excl: STEMI	1. Aspirin + Clopidogrel 300 mg loading dose followed by 75 mg daily for 3–12 mo 2. Aspirin + Placebo	• Composite: death, nonfatal MI, stroke • Bleeding (as defined by trial)	n=12,562 ~67% with ECG changes Only ~36% receiving revascularization (PCI + CABG) and ~20% receiving PCI	• Composite: Clopidogrel 9.3% vs. 11.4% (p<0.001) • Major Bleeding (trial-defined): Clopidogrel 3.7% vs. 2.7% (p=0.001)
CLARITY (2005)	Incl: STEMI receiving fibrinolytics Excl: High risk of bleeding, including age > 75	1. Clopidogrel 300 mg followed by 75 mg daily until at least hospital discharge or day 8 2. Placebo	• Composite: occluded infarct-related artery, death, recurrent MI • TIMI major bleeding	n=3491 ~47% receiving tenecteplase ~30% receiving LMWH ~93% received coronary angiography	• Composite: Clopidogrel 15.0% vs. 21.7% (p<0.001) • TIMI major bleeding (30 days): Clopidogrel 1.9% vs. 1.7% (p=0.80)
ISAR-REACT 2 (2006)	Incl: NSTE ACS Excl: STEMI, hemodynamic instability, pericarditis, high risk of bleeding incl oral anticoagulation	1. Clopidogrel 600 mg (at least 2 hr before PCI) + placebo and intra-procedural heparin 2. Clopidogrel 600 mg (at least 2 hr before PCI) + abciximab and intra-procedural heparin	• Composite: death, MI, urgent target vessel revascularization (30 day) • TIMI major bleeding (30 day)	n=2022 ~25% with prior MI ~50% troponin-positive ~50% receiving DES	• Composite: Abciximab 8.9% vs. 11.9% (p=0.03) • Composite (troponin-negative): Abciximab 4.6% vs. 4.6% (p=0.98) • TIMI major bleeding: Abciximab 1.4 % vs. 1.4% (p=NS)
TRITON (2007)	Incl: All patients with ACS intended for PCI Excl: Bleeding history	1. Prasugrel 60 mg followed by 10 mg daily x 15 mo 2. Clopidogrel 300 mg followed by 75 mg daily x 15 mo	• Composite: death, MI, stroke • TIMI major bleeding (non-CABG related)	n=13,608 26% STEMI 23% with diabetes 99% of patients received PCI ~47% with DES placement	• Composite: Prasugrel 9.9% vs. 12.1% (p<0.001) • TIMI major bleeding (non-CABG): Prasugrel 2.4% vs. 1.8% (p=0.03)
PLATO (2009)	Incl: All patients with ACS Excl: Concomitant strong CYP3A4 inhibitor/inducer, fibrinolysis	1. Ticagrelor 180 mg followed by 90 mg BID x 12 mo 2. Clopidogrel 300–600 mg followed by 75 mg daily x 12 mo	• Composite: death, MI, stroke • Major bleeding (as defined by trial)	n=18,624 ~60% receiving PCI ~18% receiving DES ~4% receiving CABG	• Composite: Ticagrelor 9.8% vs. 11.7% (p<0.001) • Mortality: Ticagrelor 4.5% vs. 5.9% (p<0.001) • Non-CABG TIMI major bleeding: Ticagrelor 2.8% vs. 2.2%, p=0.03
CHAMPION-PHOENIX (2013)	Incl: PCI, both elective and all ACS Excl: Fibrinolytics	1. Cangrelor 30 mcg/kg followed by 4 mcg/kg/min for 2 hr 2. Clopidogrel 300–600 mg	• Composite: death, MI, ischemia-driven revascularization, stent thrombosis at 48 hr • GUSTO severe bleeding at 48 hr	n=11,145 ~57% elective PCI ~17% STEMI ~74% received 600 mg clopidogrel ~55% received DES	• Composite: Cangrelor 4.7% vs. 5.9% (p=0.005) • Stent thrombosis: Cangrelor 0.8% vs. 1.4% (p=0.01) • GUSTO severe bleeding: Cangrelor 0.2% vs. 0.1% (p=0.44) • Any blood transfusion: Cangrelor 0.5% vs. 0.3% (p=0.16) • ACUITY major bleeding: Cangrelor 5.2% vs. 3.1% (p<0.0001) (femoral); 1.5% vs. 0.7% (p=0.04) (radial)

LMWH = low-molecular-weight heparin.

cangrelor administration because of its longer half-life relative to the active metabolites of the thienopyridines.

NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Non–ST-segment elevation acute coronary syndromes can be classified as UA or NSTEMI and are treated with either an "early invasive strategy" or an "ischemia-guided strategy." In an early invasive strategy, the decision is made to perform coronary angiography and PCI, typically within 24 hours of hospital admission, whereas an ischemia-guided strategy (also known as a conservative strategy or medical management) uses optimizing medications to decrease further ischemia, reduce angina, and prevent complications of ischemic heart disease, such as arrhythmias and myocardial remodeling (Amsterdam 2014). Both strategies use antiplatelet and anticoagulant agents to treat ACS.

Early Invasive Strategy

Pre-procedure

Antithrombotic therapies in patients with NSTE ACS parallel therapies in patients with STEMI in many ways. Stable patients with NSTE ACS undergoing an early invasive strategy typically do not receive an emergency PCI, in contrast to patients with STEMI. This creates a defined pre-procedural period in which the patient receives various antithrombotic therapies before undergoing PCI. As with STEMI, aspirin therapy (81–325 mg) is the recommended initial treatment before cardiac catheterization (Amsterdam 2014). The $P2Y_{12}$ inhibitors are also recommended, though using pre-procedural $P2Y_{12}$ inhibition to more completely inhibit platelet-driven thrombosis remains controversial, despite the extended pre-procedural window. The superiority of earlier $P2Y_{12}$ inhibition has not been thoroughly demonstrated to be of value in clinical trials of patients with NSTE ACS (Montalescot 2014; Steinhubl 2002). Recovery of platelet function is also a more significant issue in NSTE ACS, regardless of drug choice, because the presence of multivessel disease in patients with NSTE ACS may exceed 70% of cases, though fewer than 20% will actually undergo CABG (Parikh 2010; Gogo 2007). Regardless of the timing of $P2Y_{12}$ inhibitor administration, the guidelines state that it is reasonable to consider ticagrelor or prasugrel over clopidogrel in patients with NSTE ACS, given their improved ischemic outcomes (Amsterdam 2014; Wallentin 2009; Wiviott 2007). Use of intravenous antiplatelet agents such as "upstream" GPIs (i.e., pre-procedural GPI use outside the cardiac catheterization laboratory) for NSTE ACS should be limited, given evidence for no additional benefit with increased bleed risk (Giugliano 2009). No data currently exist with cangrelor in the pre-procedural setting of NSTE ACS.

Patients with ACS also benefit from parenteral anticoagulant therapy up until revascularization. Options include UFH,

enoxaparin, fondaparinux, and bivalirudin (see Table 1-3). Unfractionated heparin has been shown to reduce ischemic outcomes compared with no anticoagulant therapy, albeit inconsistently (Oler 1996). In lower-risk patients not receiving immediate revascularization, UFH should be continued for up to 48 hours or until PCI is performed (Amsterdam 2014; O'Gara 2013).

Enoxaparin is an attractive anticoagulation option that does not require routine monitoring. The SYNERGY trial compared enoxaparin with UFH in over 10,000 patients with NSTE ACS intended to have early invasive management and provided some salient clinical pearls (Ferguson 2004). Overall, enoxaparin did not reduce the rates of death and MI, but it did increase major bleeding. However, this may have been influenced by patients who received UFH before randomization. Subanalyses suggested that enoxaparin was superior in patients who did not receive UFH before study enrollment. Crossover from one agent to another worsened efficacy and safety outcomes in both arms and should be avoided. Some concerns with enoxaparin use include dose adjustments in renal dysfunction and possibly patients with morbid obesity, as well as evaluating the need for an additional intravenous dose before PCI, depending on the precise time when the last subcutaneous dose was given, which may not always be known.

Two other possible anticoagulant options include fondaparinux and bivalirudin. In OASIS-5, the synthetic polysaccharide factor Xa inhibitor, fondaparinux, at a low dose (2.5 mg daily) was compared with enoxaparin in over 20,000 patients with NSTE ACS and showed noninferiority in ischemic outcomes while lowering major bleeding (OASIS-5 Investigators 2006). However, the greatest concern with fondaparinux is an increase in procedural cardiac catheter thrombosis. Guidelines recommend that if fondaparinux is initially selected, another adjunct anticoagulation with anti-factor II activity be used during PCI (O'Gara 2013). Data from the FUTURA/OASIS-8 trial generally supports the use of standard dose procedural unfractionated heparin (85 units/kg or 60 units/kg if using GPI titrated to goal ACT range) compared with lower doses of heparin (FUTURA/OASIS-8 Trial Group 2010). Bivalirudin, a direct thrombin inhibitor, is capable of binding to both free and clot-bound thrombin. Although it has not been formally studied in NSTE ACS outside the PCI setting, bivalirudin can be used in place of UFH and low-molecular-weight heparin in patients with a history of HIT.

Intra-procedure

Peri-procedural management of antithrombotic therapies in NSTE ACS is very similar to management of STEMI. All patients should have received aspirin and possibly a $P2Y_{12}$ inhibitor if preloaded before PCI. If the patient was not given a $P2Y_{12}$ inhibitor, one should be given unless angiography identifies the need for CABG surgery. As with STEMI, GPIs are

typically only used in a bailout setting because the perceived need for aggressive intra-procedural antiplatelet therapy may be diminished by P2Y$_{12}$ inhibitor preloading. However, the ISAR-REACT 2 trial, in which patients with NSTE ACS undergoing PCI with clopidogrel preloading received either abciximab or placebo, showed superiority in reducing adverse cardiovascular outcomes with the planned use of GPIs (see Table 1-6).

Anticoagulant therapy is indicated in PCI, typically at higher doses to provide more intense antithrombotic therapy during the procedure. Options for anticoagulants include UFH, enoxaparin, fondaparinux, and bivalirudin. If enoxaparin was chosen as the anticoagulant before PCI, it may be used as the sole anticoagulant peri-procedurally, though the timing of dosing needs attention. If the prior subcutaneous dose was given 8–12 hours before PCI or only a single subcutaneous dose was given, an extra 0.3-mg/kg intravenous dose should be given at the time of PCI (Amsterdam 2014). Although fondaparinux is an option for NSTE ACS, its use alone is not recommended for PCI because of a higher risk of catheter thrombosis (OASIS-5 Investigators 2006).

Evidence for bivalirudin stems from the ACUITY study, in which it was compared with either UFH or enoxaparin in patients with NSTE ACS undergoing PCI (Stone 2006). Bivalirudin showed superiority to UFH/enoxaparin for the primary outcome, a combined bleeding/ischemic outcomes end point. However, this was driven primarily by decreased bleeding because ischemic outcomes were numerically higher in bivalirudin, though still meeting a generous prespecified noninferiority margin of 25%. Of note, the major bleeding definition was very liberal, likely affecting the results. Newer data from ISAR-REACT 4 show decreased bleeding with bivalirudin versus heparin with abciximab using a more stringent definition, though it was underpowered to detect a potential worsening of ischemic outcomes with bivalirudin (Kastrati 2011).

CABG Surgery

Some patients with ACS will require cardiac surgery for definitive coronary revascularization. Coronary artery bypass grafting surgery involves using an artery or vein from the patient and creating an anastomosis from the aorta distal to a coronary lesion in order to restore blood flow to that area of the myocardium. Even though the CABG surgery rates have declined recently, it remains a common approach to cardiac revascularization (Epstein 2011). The guidelines recommend CABG surgery over PCI in various clinical scenarios. Although each decision is complex and patient-specific, some common indications for CABG surgery include patients with 50% or greater stenosis of the left main coronary artery, 70% or greater stenosis of three major coronary arteries, and 70% or greater stenosis of the proximal left anterior descending artery plus another major coronary artery. Coronary artery bypass grafting surgery is also recommended in patients

with MI-associated mechanical complications (e.g., ventricular septal rupture, papillary muscle rupture).

Antithrombotic therapy from the onset of ACS to surgery, if necessary, involves balancing ischemic risks from further myocardial necrosis and complications of MI compared to bleeding risk during surgery. Additionally, some time-allowance for testing to ensure appropriate risk stratification for surgical candidacy is often necessary. In general, parenteral anticoagulants are continued up until the time of surgery with a period of offset immediately before surgery to allow for safe incision. This strategy is not necessarily evidence based but is commonly applied, despite no proven benefit to the patient and possible risk. Antiplatelet bridging is more complex, though recent drug approvals provide further options. However, few data exist describing the risk of thrombosis in an unrevascularized patient awaiting CABG, and no data regarding the patient populations to target. Many surgeons consider operating under the exposure of oral P2Y$_{12}$ inhibitors to be contraindicated and appropriate offset commensurate with their pharmacodynamic effect is warranted (5–7 days). However, platelet function recovery can be variable. Some data exist with timing surgery respective to normalized platelet function may serve to shorten the time to operation with minimal risk of bleeding compared with the label recommendations (Mahla 2012). Another option would be the use of continuous intravenous cangrelor. This therapy was investigated in the BRIDGE trial, in which patients receiving at least 72 hours of thienopyridine therapy and requiring non-emergency CABG surgery received 0.75 mcg/kg/minute or placebo until the time of surgery (Angiolillo 2012). Patients in the study (n=210) had no greater bleeding events than did patients receiving placebo. Reversible GPIs (i.e., eptifibatide) have also been used as bridging agents, though they may be associated with a greater risk of bleeding with more prolonged use.

Post-PCI Antithrombotic Therapy

After PCI, most patients are monitored closely for bleeding in an institutional setting. Current guidelines recommend cessation of anticoagulation at the end of PCI to reduce bleeding complications, with the exception of any compelling indications, such as recent venous thromboembolism or hypercoagulable state, patients with mechanical valves at high risk of thrombosis, and those requiring mechanical circulatory support (Amsterdam 2014; Levine 2011). Smaller studies of UFH have shown significantly increased bleeding with continuation of heparin after PCI (Rabah 1999). However, there has been interest in continuing bivalirudin after PCI to try to decrease the stent thrombosis seen in the aforementioned trials. Most patients in EUROMAX received post-PCI bivalirudin for at least 4 hours; nevertheless, there was an increased risk of acute stent thrombosis. However, BRIGHT continued bivalirudin as well (median duration 180 minutes), and there was no increased risk of acute stent thrombosis in

the bivalirudin arm. Neither of these studies compared post-PCI bivalirudin with a control group. The MATRIX uniquely compared post-PCI bivalirudin with placebo but found no difference in acute stent thrombosis or bleeding between the two arms. A possible explanation is that BRIGHT used full PCI doses (1.75 mg/kg/hour) post-PCI, whereas EUROMAX and MATRIX allowed for lower doses (0.25 mg/kg/hour). For patients deemed at high risk of acute stent thrombosis who received bivalirudin during PCI, continuing high-dose bivalirudin or using a GPI could be considered.

Antiplatelet therapy is a critical component of post-procedure success. Regardless of what specific procedure is performed or if an ischemia-guided strategy is chosen, all patients with ACS are recommended to receive 12 months of DAPT (Levine 2016). This is largely to reduce the risk of recurrent MI (secondary prevention), though newer agents may also reduce cardiovascular mortality. Patients who receive PCI with stent placement receive more strict guidance for minimum durations of DAPT because of the risk of in-stent thrombosis, which likely will produce an emergency coronary occlusion, if occurring. The minimum duration of DAPT for a patient receiving a BMS is 1 month, though up to 12 months is both beneficial and generally recommended. Patients post-DES placement will receive a minimum of 12 months of DAPT with a lesser recommendation to continue beyond 12 months at the cardiologist's discretion because some patients continue to be at risk of late in-stent thrombosis for years after DES placement (Levine 2016). Others may be at prolonged risk of bleeding events with lengthened treatment. To address this disparity, the DAPT trial was the largest trial examining the population-level recommended duration and randomized over 20,000 patients to 12 or 30 months of DAPT after PCI (Mauri 2014). Overall, the population risk of adverse cardiovascular events was reduced with 30 months of DAPT, whereas the rate of moderate or severe bleeding events and mortality increased. However, the mortality increase may be explained through excessive cancer-related mortality in the extended-treatment arm. This suggests that some patients or subgroups will benefit from extended therapy but that no uniform population-level recommendation can be applied.

Other studies examine short-term interruptions or premature discontinuation, like those that critically ill patients may have because of surgery or other factors. The SENS trial showed that of 194 patients post-DES who required discontinuation of DAPT for procedures, only 4 (2.2%) had significant cardiovascular events (Kim 2009). Similarly, in the DATE registry, 823 patients (not including higher-risk PCI procedures) discontinued P2Y$_{12}$ inhibitor therapy after 3 months (Hahn 2010). Cardiovascular outcomes and stent thrombosis events were less than 0.5% at 12 months. Although intriguing, further data are needed regarding whether a short-term interruption or premature discontinuation in a low-risk patient is safe before any definitive recommendation can be made. The risks to the patient (cardiovascular outcomes/events vs. bleeding)

should be determined on a patient-specific basis. Because this may depend on procedural factors, consultation with an interventional cardiologist to determine the appropriate duration of DAPT is highly recommended. Risk scores may also aid in decision-making (Baber 2016; Kereiakes 2016).

Ischemia-Guided Strategy

Antiplatelet therapies benefiting patient populations in an ischemia-guided strategy are not significantly different from those in other ACS settings that receive revascularization. These patients still benefit from DAPT for up to 1 year post-event. The usefulness of more potent P2Y$_{12}$ inhibitors in addition to aspirin in patients with ACS who do not receive PCI is inconsistent. This was shown in the TRILOGY-ACS trial, in which prasugrel failed to improve ischemic outcomes compared with clopidogrel in this patient population (Roe 2012). However, ticagrelor had benefit over clopidogrel in PLATO, regardless of management strategy, and is preferred to clopidogrel in the guidelines for an ischemia-guided strategy (Amsterdam 2014; Wallentin 2009).

Parenteral anticoagulant agents also provide value in an ischemia-guided strategy. Options include intravenous UFH at a 60 units/kg bolus with an initial infusion of 12 units/kg/hour titrated to a therapeutic aPTT or anti-Xa, enoxaparin 1 mg/kg subcutaneously every 12 hours, and fondaparinux 2.5 mg subcutaneously daily. Unfractionated heparin is recommended to be continued for 48 hours, whereas enoxaparin and fondaparinux are recommended to be continued for the duration of the hospital stay. If, however, the decision is later made to undergo PCI, these agents should be discontinued afterward. Guidelines do not give any preference to one agent over another (Amsterdam 2014). Enoxaparin has been compared with UFH in various studies, showing a significant reduction in ischemic outcomes (Antman 1999; Cohen 1997; Blazing 2004). However, most of these studies were conducted before modern-era P2Y$_{12}$ inhibitors, which limits them. Fondaparinux was studied in the previously mentioned OASIS-5 trial, which included both patients who underwent an early invasive strategy and those who underwent an ischemia-guided strategy. Fondaparinux was noninferior to enoxaparin with a decreased incidence of bleeding, though this may be related to the lower-intensity dosing strategy in the fondaparinux arm.

MANAGEMENT OF CHRONIC ANTITHROMBOTIC PHARMACOTHERAPY

The management of chronic antithrombotic pharmacotherapy prescribed for coronary artery disease in a patient who presents with unrelated critical illness is complex. Dual antiplatelet therapy may increase the risk of bleeding when various diagnostic or invasive procedures are indicated. Dual antiplatelet therapy may also increase the risk

of major and life-threatening bleeding events, resulting in critical illness. Balanced against this, critically ill patients are at greater risk of ischemic coronary events which lead to greater risk of mortality if they occur. Premature cessation of DAPT increases the risk of coronary events. In addition, the contribution of DAPT to various procedural risks is largely unknown and may be overstated. The appropriate management, therefore, must balance the risk of bleeding with the thrombosis events in the specific patient. However, several population-level studies provide greater insight into treating the individual patient.

The principal factors that aid the clinician in assessing the risk of coronary thrombosis are whether a stent or several stents were placed in a coronary artery, the type of stent (BMS vs. DES), and the duration from the index event, with earlier times conferring higher risk. Lesser, but potentially important factors include the specific location of the stent in an artery, the myocardial territory affected, procedural factors such as the use of overlapping stents, bifurcation lesions, and the length of stent chosen. Ideally, all antithrombotic therapy prescribed for either secondary prevention or prevention of coronary stent thrombosis should be continued in a critically ill patient in the absence of contraindications. The consequences of stent thrombosis tend to be quite severe, resulting in death or MI in over 60% of patients (Cutlip 2001). However, when faced with higher bleeding risk scenarios or critical illness related to bleeding events, several additional scenarios may be considered. In the absence of coronary stents, DAPT used for secondary prevention likely can be temporarily held or at least minimized to aspirin only to provide a balance of protection versus bleeding risk. In a patient with coronary stents, $P2Y_{12}$ inhibitors can generally be temporarily held after 1 month after BMS placement and 12 months after DES placement. Because very late stent thrombosis still occurs with DES, some patients may be recommended for lifetime DAPT. It is therefore recommended to engage cardiologists in this discussion, if possible, even if stent placement occurred more than 12 months earlier. In a patient with a high risk of bleeding or an active bleeding event, guidelines generally suggest discontinuing DAPT after 2 weeks of therapy post-BMS and 6 months of DES therapy may be safe, though again, these decisions should be made in concert with cardiology consultation (Levine 2016). A patient for whom DAPT must be discontinued secondary to life-threatening bleeding should receive consultation with cardiology to determine the best course of action. Use of aspirin-only regimens in these scenarios may provide the best balance of bleeding versus protection. In the STARS trial, electively placed, older-generation coronary stents protected with aspirin only (325 mg/day) produced a 30-day event rate of adverse cardiovascular effects of 3.6% (Leon 1998). Although inferior to a regimen containing DAPT, this may provide an acceptable approximation of risk if faced with a catastrophic bleeding scenario.

MANAGEMENT OF ADVERSE EFFECTS FROM ANTITHROMBOTIC PHARMACOTHERAPY

Bleeding

Although coronary thrombosis can be catastrophic, the negative effects of bleeding associated with antithrombotic therapy should not be underestimated. Although previously seen as simply an undesired adverse effect, bleeding has been shown to be associated with increased morbidity and mortality, and is now regarded as an important clinical outcome (Steg 2011). Some possible explanations for this include prolonged cessation of antiplatelet therapy, endogenous prothrombotic rebound, and increased sympathetic response resulting in myocardial ischemia. Risk factors for bleeding include older age, female sex, lower body weight, invasive procedures, renal insufficiency, and history of bleeding. Newer oral $P2Y_{12}$ agents, GPI, triple therapy with DAPT and an anticoagulant, and antithrombotic agents not adjusted for renal dysfunction all increase the risk of bleeding.

Strategies to reduce the risk of bleeding should include carefully selected patients for invasive procedures, consideration for delaying procedures in patients with lower ischemic risk and high bleed risk (e.g., non-urgent CABG surgery for patient who just received a $P2Y_{12}$ inhibitor). Procedural techniques can reduce bleeding risk, such as radial artery approaches to PCI versus femoral approaches. As mentioned previously, the radial artery approach to PCI access site decreases the incidence of bleeding and is quickly becoming more prevalent in select centers. This selection of access site may also influence post-PCI decisions as they relate to the risk of bleeding. For example, the risk of continuing anticoagulation post-PCI may be higher in someone who underwent a femoral artery approach versus a radial artery approach.

Antithrombotic medications clearly affect bleeding risk, and many considerations need to be made to minimize that risk. Appropriate selection, dosing, and duration of antithrombotic medications are fundamental to reducing bleeding risks. The $P2Y_{12}$ inhibitors may have varying efficacy and safety in different populations, such as the increased risk of bleeding of prasugrel over clopidogrel without improved efficacy in patients with NSTE ACS treated with an ischemia-guided strategy (Roe 2012). Thus, proper selection of agents can help minimize unnecessary risk of excess bleeding. For patients with a high risk of bleeding undergoing PCI, either the use of bivalirudin or the avoidance of GPI may be warranted. Triple antithrombotic therapy with aspirin, a $P2Y_{12}$ inhibitor, and an anticoagulant significantly increases the risk of bleeding and should be avoided, when possible. Many antithrombotic medications need dose adjustments or drug avoidance based on renal function (see Table 1-3) or other variables such as age and weight (prasugrel, apixaban). All current guidelines prefer aspirin 81 mg to higher doses as this has been shown to have equal efficacy with reduced GI bleeding

(CURRENT-OASIS 7 Investigators 2010). Reducing the duration of DAPT can decrease bleeding and should be considered. Finally, patients at risk of GI bleeding (e.g., history of GI bleed, GI ulcers, triple antithrombotic therapy) may benefit from a proton pump inhibitor given with antithrombotic therapy (Amsterdam 2014; Vaduganathan 2016). Although some concerns may exist with a pharmacodynamic drug interaction between omeprazole and clopidogrel, clinical outcomes have not been affected (Bhatt 2010; Dunn 2013). Any decision to interrupt or discontinue antithrombotic therapies needs to weigh carefully the risks of ischemic complications versus the risks of bleeding. For mild to moderate bleeds, if the patient is still in the guideline-recommended period of mandatory DAPT, both drugs should be continued with supportive management for the acute bleed. Major bleeding may require interruption of DAPT, regardless of the timing of stent placement. For all bleeds, supportive care and specific interventions should be made to promote hemostasis, if available (e.g., fluids, blood products, endoscopic GI repair, manual pressure of an access site, topical vasoconstrictors and packing of epistaxis) (Steg 2011).

Other Severe Adverse Effects

Thrombocytopenia

Registries of patients with ACS have shown the incidence of thrombocytopenia as 1.6%–13%, depending on the definition of thrombocytopenia (Gore 2009; Wang 2009). They have also shown increased mortality in patients who develop thrombocytopenia, as well increased bleeding and reinfarction. Thus, monitoring platelets in these patients is critical/necessary. Various antithrombotic medications can lead to thrombocytopenia.

The GPIs are most likely to cause thrombocytopenia. It can occur in up to 0.4%–5.2% of patients undergoing PCI with abciximab, whereas eptifibatide and tirofiban have a lower incidence of 0.5%–3.2% (Matthai 2010). However, the true incidence of thrombocytopenia with all GPIs is often confounded by heparin use. Although use of these agents has decreased, it is prudent to recognize their adverse effects. Thrombocytopenia occurs early after initiating the drug, and platelets should be monitored 2–4 hours afterward. If thrombocytopenia is present, drug discontinuation is recommended to prevent profound thrombocytopenia. Patients who have experienced this should not be reinitiated on a GPI in the future, if possible. Should there be an acute indication, a different GPI should be used to avoid the risk of repeat thrombocytopenia. Thienopyridines such as ticlopidine, clopidogrel, and prasugrel have been associated with thrombocytopenia as well. Ticlopidine was rarely used because of its higher incidence of adverse effects, which include thrombotic thrombocytopenic purpura, a microangiopathic hemolytic anemia, and has been removed from the U.S. market. Clopidogrel and prasugrel can also cause thrombotic thrombocytopenic purpura, but it is very rare.

Patient Care Scenario

M.A. is a 69-year-old woman found in her bathroom after a fall; she appears to have a head injury. Her medical history consists of hypertension, type 2 diabetes, dyslipidemia, coronary artery disease with two DES placed in her mid-right coronary artery 4 months ago, and arthritis. On arrival at the ED, she seizes and is intubated for airway protection. A CT scan of her head reveals a large intracranial hemorrhage (ICH). An emergency neurosurgery consult is placed. Which one of the following is the most appropriate urgent management of M.A.'s stent antithrombotic therapy?

    A. Discontinue both aspirin and clopidogrel.
    B. Continue aspirin, but discontinue clopidogrel.
    C. Continue clopidogrel, but discontinue aspirin.
    D. Continue both aspirin and clopidogrel, given her recent stent placement.

ANSWER:

Although interrupting DAPT is highly discouraged within the first 6–12 months of DES placement, it must be considered in severe circumstances. An ICH is a devastating major bleed because it cannot be compressed and can cause rapid, permanent damage if not controlled. There are few data to guide clinicians in these situations, and management is based largely on expert opinion (ideally with both an interventional cardiologist and a neurosurgeon). In less severe non-ICH bleeds and when duration of DAPT is complete or near-complete, continuing aspirin only and discontinuing the P2Y$_{12}$ agent can be considered. The decision is more challenging in more severe bleeds, or if stents were recently placed, and should be made on a patient-specific basis. When the ICH has led to seizures and intubation, discontinuing both agents is necessary. Discontinuing DAPT will likely increase the risk of stent thrombosis. However, continuing antithrombotic therapy poses a definite, real risk of an exacerbating the life-threatening bleed. In conjunction with a neurosurgery or neurology consultation, if it appears clinically and radiologically that the ICH has stabilized, reinitiating aspirin and sequentially (if indicated) the P2Y$_{12}$ inhibitor can then be considered.

1. Flower O, Smith M. The acute management of intracerebral hemorrhage. Curr Opin Crit Care 2011;17:106-14.
2. Okada T, Nakase T, Sasaki M, et al. Do the antithrombotic therapy at the time of intracerebral hemorrhage influence clinical outcome? Analysis between the difference of antiplatelet and anticoagulant agents and clinical course. J Stroke Cerebrovasc Dis 2014;23:1781-8.

Heparin-induced thrombocytopenia is another rare form of thrombocytopenia that may occur in any patient exposed to heparin products. Endogenous platelet factor 4 (PF4) binds to heparin in the plasma. Heparin-induced thrombocytopenia can occur when these PF4-heparin complexes form antibodies that then bind to platelets, causing platelet activation, aggregation, clot formation, and consumptive thrombocytopenia. Acute coronary syndrome registries have reported a 0.3% incidence in patients with ACS (Gore 2009). The incidence is likely higher in cardiac surgery patients because of large amounts of intraoperative heparin exposure and PF4 release ranging from 1%–3% (Matthai 2010). Heparin-induced thrombocytopenia is characterized by a decline in platelets to less than 150,000/mm^3 or a 50% decrease from baseline, occurring 5–14 days after heparin exposure. Unlike GPI-associated thrombocytopenia in which the platelet nadir is typically 20,000/mm^3, HIT platelet nadirs are typically closer to 50,000/mm^3. This platelet reduction can also occur within 1 day if patients have had exposure within the past 100 days. Although these timelines may overlap with thrombocytopenia occurring with thienopyridines, severe bleeding associated with GPI-associated thrombocytopenia usually does not occur in HIT and can help distinguish the diagnosis as well as the timing and nadir of the platelet decrease. Although laboratory testing may help diagnose HIT, it is ultimately a clinical diagnosis. If suspicion is high, all heparin products must be discontinued (including low-molecular-weight heparin, heparin flushes, and heparinized catheters), and a direct thrombin inhibitor should be initiated to prevent thromboses. A complete discussion of the evaluation and treatment of HIT is beyond the scope of this chapter, but bivalirudin use is preferred with a history of HIT or if HIT is suspected and anticoagulation is indicated because of the clinical trial data associated with bivalirudin in patients with ACS.

Other Adverse Effects

Ticagrelor and cangrelor cause some unique adverse drug reactions, such as dyspnea and bradycardia, as a result of their structural relationship with adenosine. Dyspnea is a common symptom of many disease states and can potentially be a warning sign for disease exacerbation. In the cardiac patient, dyspnea of heart failure may be a presenting sign of worsening ischemia or progressive heart failure. Clinicians must be prudent in assessing the cause of dyspnea, as it may allow for an opportunity to intervene before a patient decompensates. Unfortunately, dyspnea has a very broad differential diagnosis with many triggers, including non–disease-related triggers. The mechanism of P2Y$_{12}$ inhibitor–induced dyspnea is controversial. Some argue that ticagrelor prevents adenosine reuptake and promotes adenosine-induced dyspnea, though this theory has been debated (van den Berg 2015). The incidence and consequence of dyspnea related to ticagrelor and cangrelor is not well defined. Since it was identified, many studies have described an increased risk of dyspnea

with both agents (Cattaneo 2012; Wallentin 2009; Bhatt 2013). These studies have shown that dyspnea with ticagrelor may occur within 24 hours to 7 days after initiation, and in the clinical trials, it occurred in about 15%–38% of patients (Sanchez-Galian 2015; Cattaneo 2012). Although the dyspnea is typically mild to moderate, it can be severe enough to require drug discontinuation in up to 4% of patients. If needed, discontinuation of ticagrelor typically occurs in the first 1–2 weeks (Bonaca 2015). There are no well-defined recommendations for ticagrelor-induced dyspnea, though most cases do not require drug discontinuation. All other causes of dyspnea must first be ruled out. It may be challenging to distinguish dyspnea of cardiac etiology versus drug-induced dyspnea in a patient with a recent MI. If dyspnea is thought to be the result of a specific disease process, the presence or absence of other clinical features may help narrow the etiology. Currently, no treatments exist for ticagrelor-induced dyspnea. If identified, ticagrelor may need to be discontinued and replaced with another P2Y$_{12}$ inhibitor.

Bradycardia and other bradyarrhythmias have also been identified in ticagrelor-treated patients, presumably because of an adenosine-related effect. In the PLATO trial, ticagrelor-treated patients receiving continuous ECG monitoring (n=2866) had a greater frequency of asymptomatic pauses of more than 3 seconds (5.8% vs. 3.6%, p=0.01) within the first week of treatment but not at 30 days (Wallentin 2009). There was no significant difference in symptomatic events. The implications for these events are unclear, though ticagrelor should be considered in the differential for a patient with ventricular pauses or bradyarrhythmias, particularly within the first week of treatment. Ticagrelor also induces hyperuricemia, possibly through reduced uric acid clearance or increased production by adenosine, with potential implications for patients with a history of gout or other hyperuricemic disorders (Zhang 2015).

CONCLUSION

Antithrombotic therapy for critically ill patients with ACS is complex and involves many branching decision points. Even defining a true ACS compared with myocardial ischemia from preexisting critical illness is complex and not always easily definable. Management of chronic antithrombotic therapy in critically ill patient populations is equally complex. Guidelines recommend minimum durations of DAPT for secondary prevention of ACS as well as prevention of stent thrombosis if a patient receives PCI. However, patients may receive long-term or lifelong DAPT at their cardiologist's discretion. A patient-centered approach underscores the need for good communication between intensivist teams and cardiologists to determine the best management options for a given patient.

Finally, DAPT therapy and other anticoagulants are associated with adverse effects, including bleeding, thrombocytopenia, and other toxicities. Familiarity with identifying

and managing these episodes as well as the risks of discontinuing therapy is paramount in ensuring optimal patient outcomes.

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

M.J. is a 56-year-old man with a medical history significant for coronary artery disease; he had a percutaneous coronary intervention (PCI) with stent placement to the proximal left circumflex sometime in the past 12 months after having stable angina symptoms refractory to medical therapy. M.J. presents at the ED today with a several-week history of coffee-ground emesis and dark, tarry stools. This morning, he felt dizzy and had presyncopal events together with chest pain. His hemoglobin is 5.3 g/dL on admission, blood pressure is 80/60 mm Hg, and heart rate is 95 beats/minute. M.J. is admitted to the medical ICU for further treatment. His ECG is significant for ST depressions in the anterolateral leads. His first troponin is 1.25 ng/mL, which increases to 2.5 ng/mL 6 hours later. His home drugs include aspirin 325 mg daily, clopidogrel 75 mg daily, lisinopril 5 mg daily, and metoprolol tartrate 25 mg twice daily.

1. According to the universal definition of MI, which one of the following types of infarction is most consistent with M.J.'s presentation?

    A. 1
    B. 2
    C. 3
    D. 4

2. M.J. is given a medical diagnosis of, and meets the criteria for, a non–ST-segment elevation myocardial infarction (NSTEMI). Which one of the following would be the most appropriate anticoagulation therapy to promote clot stabilization until reperfusion and/or further testing modalities can be initiated for M.J.?

    A. Give unfractionated heparin (UFH).
    B. Give enoxaparin.
    C. Give fondaparinux.
    D. Anticoagulation therapy is not necessary.

3. Which one of the following best describes the optimal management of M.J.'s chronic dual antiplatelet therapy (DAPT) in the acute setting?

    A. Discontinue clopidogrel and continue aspirin.
    B. Discontinue aspirin and clopidogrel.
    C. More information is needed about the patient's stent.
    D. Continue both aspirin and clopidogrel.

Questions 4–6 pertain to the following case.

J.M., a 65-year-old man with a history of tobacco abuse, hypertension, type 2 diabetes, peripheral arterial disease, and seizure disorder secondary to traumatic brain injury, presents to the ED with persistent chest pain. In the ED, his chest pain is fairly refractory to continuous nitroglycerin, and he is transferred to the CCU for closer monitoring. J.M.'s ECG is consistent with diffuse ST depression and slight ST-elevation (non-STEMI criteria) in aVR, suggestive of disease in the left main coronary artery. Troponin is elevated at 1.5 ng/mL. His home drugs include aspirin 81 mg daily, metformin 1000 mg twice daily, metoprolol 50 mg twice daily, and phenytoin 300 mg at bedtime. J.M. received enoxaparin 1 mg/kg subcutaneously x 1 dose in the ED. His vital signs include blood pressure 100/60 mm Hg and heart rate 72 beats/minute.

4. According to the universal definition of MI, which one of the following types of infarction is most consistent with J.M.'s presentation?

    A. 1
    B. 2
    C. 3
    D. 4

5. The team is concerned that J.M. may have left main coronary disease, given his ECG findings, and therefore may require urgent cardiac surgery if identified through coronary angiography. Given this concern, which one of the following antiplatelet regimens is most appropriate while J.M. awaits cardiac catheterization (expected within 1 hour)?

    A. Continue his aspirin therapy only.
    B. Administer 60 mg of prasugrel, followed by 10 mg daily.
    C. Administer 180 mg of ticagrelor, followed by 90 mg twice daily.
    D. Initiate cangrelor at 0.75 mcg/kg/minute continuous intravenous infusion.

6. Which one of the following is the most appropriate action regarding J.M.'s anticoagulation therapy?

    A. Discontinue all anticoagulation, given his potential for upcoming cardiac surgery.
    B. Administer UFH (60-unit/kg bolus, followed by 12 units/kg/hour infusion) immediately on arrival at the critical care ICU.
    C. Continue therapeutic enoxaparin with the next dose 12 hours from his first dose in the ED.
    D. Change to fondaparinux 2.5 mg subcutaneously daily (first dose the following day) to reduce his risk of bleeding.

7. A 59-year-old woman presents for an emergency appendectomy after complaints of abrupt-onset abdominal pain. She has a history of coronary artery disease, including stenting of her left circumflex artery 8 months ago with drug-eluting stent (DES) placement (specific stent unknown). In addition, she has a medical history

of hypertension, tobacco abuse, and obesity. Her home drugs include aspirin 81 mg daily, clopidogrel 75 mg daily, atorvastatin 40 mg daily, and paroxetine 20 mg daily. Her surgery is relatively uncomplicated, and she is admitted to the surgical ICU postoperatively for monitoring. Which one of the following is best to recommend for this patient's antiplatelet therapy in the acute post-surgical setting?

A. Discontinue both aspirin and clopidogrel because of the risk of bleeding.
B. Discontinue aspirin and clopidogrel, and initiate cangrelor at 0.75 mcg/kg/minute.
C. Continue her home aspirin and clopidogrel if surgical risk is not prohibitive.
D. Discontinue clopidogrel but continue aspirin therapy.

Questions 8–10 pertain to the following case.

K.L. is a 45-year-old man admitted with acute onset substernal chest pain. His medical history is consistent with end-stage renal disease on hemodialysis, type 2 diabetes, peripheral arterial disease with a femoral-popliteal bypass, hypertension, tobacco abuse, and carotid artery disease. K.L.'s ECG is significant for ST-segment depression in anterolateral leads with reciprocal changes in inferior leads. His initial troponin is 2.6 ng/mL, and he is placed on the cardiac ICU because of refractory chest pain. Given his other atherosclerotic disease and related risk factors, the cardiology team is concerned that K.L. may have multivessel coronary disease that would be best managed with cardiac bypass surgery. However, he is scheduled for cardiac catheterization tomorrow morning for a definitive diagnosis and potential PCI, should he have treatable disease. K.L. has received aspirin from the ED.

8. Which one of the following is the best option to initiate for K.L.'s anticoagulation therapy?

A. Fondaparinux
B. Bivalirudin
C. Enoxaparin
D. UFH

9. K.L. has coronary disease in three discrete arteries, best treated with coronary artery bypass grafting (CABG) surgery. He undergoes a workup regarding his candidacy for surgery. A few days later, he develops thrombocytopenia with a greater than 50% drop in platelet count from a baseline of 300,000/mm^3 to 128,000/mm^3. The team sends laboratory monitoring, including platelet factor 4 and serotonin release assay, which will have a minimum of 48 hours' turnaround. Which one of the following is the most appropriate action regarding K.L.'s anticoagulation?

A. Discontinue heparin, begin enoxaparin at 1 mg/kg subcutaneously every 12 hours.

B. Continue heparin and initiate cangrelor at 0.75 mcg/kg/minute.
C. Discontinue heparin and initiate eptifibatide at 2 mcg/kg/minute.
D. Discontinue heparin and initiate therapeutic bivalirudin, titrated to therapeutic aPTT.

10. K.L.'s dynamic chest pain continues after the procedure. The team is trying to expedite his surgery. In the interim, they wish to initiate some antiplatelet therapy as a bridge to surgery. Which one of the following is best to recommend for K.L.?

A. Initiate eptifibatide at 2 mcg/kg/minute.
B. Load with 180 mg of ticagrelor x 1.
C. Load with 60 mg of prasugrel x 1.
D. Initiate cangrelor at 0.75 mcg/kg/minute.

11. Your hospital receives a call for potential transfer from a rural hospital. A 68-year-old man presented to the ED with complaints of nausea, vomiting, and diaphoresis. His medical history includes hypertension (reportedly well controlled with current blood pressure 135/75 mm Hg and heart rate 90 beats/minute) and dyslipidemia. Fifteen minutes after being seen by paramedics, his ECG showed ST elevations in leads V2–V5. He was immediately given aspirin, enoxaparin, and nitroglycerin. The ED physician at the outside hospital consults with your cardiologist about potentially transferring the patient for cardiac catheterization versus giving fibrinolytic therapy. The patient has no known contraindications for fibrinolytics. The patient's estimated travel time is 55 minutes. Which one of the following is best to recommend for this patient?

A. Give clopidogrel 300 mg now plus tenecteplase; then have the patient transferred to your center for cardiac catheterization.
B. Give clopidogrel 600 mg now plus tenecteplase; then have the patient transferred to your center for cardiac catheterization.
C. Give clopidogrel 300 mg and have the patient immediately transferred to your center for cardiac catheterization.
D. Give clopidogrel 600 mg and have the patient immediately transferred to your center for cardiac catheterization.

Questions 12 and 13 pertain to the following case.

G.G. is a 44-year-old man who presents to your ED with the chief concern of crushing chest pain. He has ST elevations in leads V3 and V4 and receives a diagnosis of a STEMI. His medical history includes hypertension; he is otherwise healthy. G.G. is given aspirin 325 mg once and heparin 5000 units intravenously once, and he is taken emergently to the cardiac catheterization laboratory for a primary PCI.

12. Which one of the following is the best anticoagulation strategy to recommend for G.G.?

   A. Enoxaparin 1 mg/kg subcutaneously once
   B. Fondaparinux 2.5 mg intravenously once
   C. Bivalirudin 180 mcg/kg double bolus
   D. No anticoagulant needed unless the ACT is below goal

13. G.G. received 60 mg of prasugrel during PCI as well as bailout abciximab for slow flow after revascularization. Two hours after arriving at your ICU, he continues to bleed from his access site. A CBC is normal except for a platelet count of 26,000/mm^3. G.G.'s baseline platelet count on admission was within normal limits. Which one of the following drugs most likely caused G.G.'s thrombocytopenia?

   A. Aspirin
   B. Abciximab
   C. Heparin
   D. Prasugrel

14. A 76-year-old man presents to your hospital for an inguinal hernia repair. He has a medical history of hypertension, dyslipidemia, and remote MI treated with a DES several years earlier (unknown vessel and no longer taking P2Y$_{12}$ inhibitor). On postoperative day 1, the patient develops chest pain. An ECG shows ST depressions in leads V1–V3. The patient is given aspirin, clopidogrel, and heparin. He then experienced pulseless ventricular tachycardia. Cardiopulmonary resuscitation is initiated, and the patient is successfully resuscitated and transferred to your ICU. He then has hematemesis and hypotension, prompting the team to hold clopidogrel. Three days later, the patient has no longer had any bleeding, and his hemoglobin and hemodynamics are stable. An EGD reveals friable mucosa but no obvious signs of bleeding. Which one of the following is best to recommend regarding this patient's P2Y$_{12}$ therapy in the acute setting?

   A. Hold clopidogrel therapy, given the recent GI bleed.
   B. Reinitiate clopidogrel.
   C. Change to prasugrel therapy.
   D. Initiate cangrelor therapy while awaiting a final decision on oral P2Y$_{12}$ therapy.

15. The DAPT trial examined the benefit and risk of 12 months of DAPT (aspirin plus clopidogrel or prasugrel) versus 30 months of DAPT in patients receiving PCI with DES. Patients received the guideline-recommended 12-month minimum duration and were then randomized to receive continued thienopyridine versus placebo up to 30 months. The primary end points of the trial were definite or confirmed stent thrombosis, a composite of major adverse cardiovascular events (death, MI, stroke), and the incidence of moderate or severe bleeding using the GUSTO scale. Outcomes are as follows:

	Thienopyridine (n=5020)	Placebo (n=4941)	Hazard Ratio (95% CI)	p value
Stent thrombosis (definite or probable), n (%)	19 (0.4)	65 (1.4)	0.29 (0.17−0.48)	< 0.001
Major adverse cardiovascular events, n (%)	211 (4.3)	285 (5.9)	0.71 (0.59−0.85)	< 0.001
GUSTO severe or moderate bleeding, n (%)	119 (2.5)	73 (1.6)	1.0 (0.4−1.5)	0.001

Using number needed to treat (NNT) versus number needed to harm (NNH), which one of the following best depicts the risk-benefit of continued DAPT when comparing stent thrombosis events (definite or probable) with the incidence of GUSTO severe or moderate bleeding?

   A. Risk-benefit is about equal.
   B. Risk is significantly greater than benefit.
   C. Benefit is significantly greater than risk.
   D. Not enough information is provided.

Questions 16–18 pertain to the following case.

J.W. is a 63-year-old man (weight 80 kg) with a medical history of alcohol abuse, cirrhosis, GI bleed (1 year ago), and poor adherence to medical care. He is admitted to the medical ICU with altered mental status, hyperammonemia, jaundice, and fluid overload. On day 2 of admission, he has complaints of chest pressure and is found to have ST-segment depressions in leads V$_1$–V$_4$. The decision is made to pursue an ischemia-guided strategy for treatment of non−ST-segment elevation acute coronary syndrome (NSTE ACS).

16. Which one of the following is the most appropriate antiplatelet regimen to recommend for J.W.?

   A   Aspirin 81 mg plus ticagrelor 90 mg twice daily
   B. Aspirin 81 mg plus prasugrel 10 mg daily
   C. Aspirin 81 mg plus clopidogrel 75 mg daily
   D. No antiplatelet therapy at this time

17. Which one of the following is the most appropriate UFH regimen to recommend for J.W.?

A. A 6400-unit intravenous bolus followed by 1440 units/hour for 48 hours

B. A 6400-unit intravenous bolus followed by 1440 units/hour for 8 days

C. A 4800-unit intravenous bolus followed by 960 units/hour for 48 hours

D. A 4800-unit intravenous bolus followed by 960 units/hour for 8 days

18. Which one of the following would best attenuate J.W.'s risk of bleeding?

A. Initiate pantoprazole continuous infusion at 8 mg/hour.

B. Initiate pantoprazole 40 mg orally daily.

C. Separate out administration times of antithrombotic drugs.

D. Give lower doses of one or more antithrombotic regimens.

19. A 55-year-old man has a medical history of STEMI (3 days ago) with an asymptomatic left ventricular ejection fraction 24 hours after the event of 40%, tobacco abuse, hypertension, and diabetes. He had two DESs placed and is awaiting hospital discharge on the acute care floor on aspirin 81 mg, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, carvedilol 12.5 mg twice daily, and lisinopril 5 mg twice daily. During morning rounds, your team receives a page that the patient is feeling short of breath. A 12-lead ECG is unchanged from his baseline. Cardiac biomarkers are negative. His lungs are clear to auscultation, and chest radiography is clear without evidence of edema or infectious processes. His Sao_2 is 99%, and his respiratory rate is 28 breaths/minute. A bedside arterial blood gas fails to identify evidence of CO_2 retention. Which one of the following is the most likely cause of this patient's symptoms?

A. Ischemic heart disease

B. Ticagrelor

C. Lisinopril

D. Acute decompensated heart failure

20. Which one of the following is most likely to result in patient harm secondary to medical error?

A. Administration of ticagrelor on an every-12-hour versus twice-daily schedule

B. Coadministration of clopidogrel with a proton pump inhibitor

C. Administration of a loading dose of clopidogrel during a cangrelor infusion in PCI

D. Administration of 600 mg of clopidogrel instead of 300 mg for a loading dose