

# **ACUTE CARE IN CARDIOLOGY**

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**Learning Objectives**

1. Distinguish between the treatments for acute coronary syndrome: ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome.
2. Formulate evidence-based treatment strategies for patients with acute decompensated heart failure.
3. Devise a treatment plan for patients presenting with ventricular or life-threatening arrhythmias.
4. Differentiate between goals and treatment for hypertensive emergencies and hypertension without progressive organ damage.

NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
SCD	Sudden cardiac death
SHD	Structural heart disease
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
UA	Unstable angina
UFH	Unfractionated heparin
VF	Ventricular fibrillation
VT	Ventricular tachycardia

**Abbreviations in This Chapter**

AAD	Antiarrhythmic drug
ACE	Angiotensin-converting enzyme
ACLS	Advanced cardiac life support
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADHF	Acute decompensated heart failure
ADR	Adverse drug reaction
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CO	Cardiac output
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
EF	Ejection fraction
GI	Gastrointestinal
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HF	Heart failure
HIT	Heparin-induced thrombocytopenia
ICD	Implantable cardioverter-defibrillator
LD	Loading dose
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MI	Myocardial infarction
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome

**Self-Assessment Questions**

*Answers and explanations to these questions may be found at the end of this chapter.*

1. A 62-year-old man presents to the emergency department (ED) with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment depression in leads II, III, and aVF. His blood pressure is 112/62 mm Hg and heart rate is 60 beats/minute. Cardiac enzymes have been obtained, and the first troponin result was slightly positive. Preparations are under way to take the patient to the cardiac catheterization laboratory for evaluation. Which medication regimen is most appropriate for this patient at this time?
  - A. Aspirin 325 mg, clopidogrel 600-mg loading dose (LD), and unfractionated heparin (UFH) infusion 80-unit/kg bolus, followed by 18 units/kg/hour and metoprolol 5 mg intravenously.
  - B. Aspirin 81 mg; prasugrel 60-mg LD; UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour; and intravenous enalaprilat.
  - C. Aspirin 325 mg, ticagrelor 180-mg LD, and UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour.
  - D. Aspirin 81 mg, prasugrel 60-mg LD, nitroglycerin infusion at 10 mcg/minute, and bivalirudin 0.75-mg/kg bolus and 1.75-mg/kg/hour infusion.

2. An 81-year-old African American man (weight 90 kg) presents to the ED with chest pressure (10/10 on a pain scale). His ECG reveals ST-segment depression in the inferior leads. His medical history is significant for hypertension and chronic kidney disease. Pertinent laboratory results are troponin 5.8 ng/L, serum creatinine (SCr) 3.7 mg/dL, and estimated creatinine clearance (eCrCl) 20 mL/minute. The patient has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. The patient consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?
  - A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.
  - B. Enoxaparin 90 mg subcutaneously every 12 hours.
  - C. Fondaparinux 2.5 mg subcutaneously daily.
  - D. Bivalirudin 67.5-mg bolus, followed by a 157-mg/hour infusion.
3. A 56-year-old man presents to the hospital with the chief concern of chest pain that was unrelieved at home with sublingual nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. The cardiologist has requested that the patient go to the cardiac catheterization laboratory for further evaluation. The patient has a history of coronary artery disease (CAD) and had a myocardial infarction (MI) about 6 months ago. During his previous hospitalization, he was confirmed to have developed heparin-induced thrombocytopenia (HIT) after his platelet count (Plt) dropped to 40,000/mm<sup>3</sup> and he had a positive ELISA (enzyme-linked immunosorbent assay) upon serologic testing after his previous catheterization. Given this patient's diagnosis and history, which treatment regimen would be most appropriate during his cardiac catheterization?
  - A. Abciximab.
  - B. Bivalirudin.
  - C. Enoxaparin.
  - D. Tenecteplase.
4. A 62-year-old man presents to the ED after several hours of chest discomfort. His ECG reveals a 1- to 2-mm ST-segment elevation with positive troponins. He has also had increasing shortness of breath and lower-extremity swelling over the past 2–3 weeks. His medical history is significant for tobacco use for 40 years, chronic obstructive pulmonary disease, diabetes, and hypertension. His blood pressure is 102/76 mm Hg and heart rate is 111 beats/minute. He has rales in both lungs and 2–3+ pitting edema in his extremities. His echocardiogram reveals an ejection fraction (EF) of 25%. After primary percutaneous coronary intervention (PCI), he is transferred to the cardiac intensive care unit. Which best describes the acute use of  $\beta$ -blocker therapy in this patient?
  - A. Give 12.5 mg of oral carvedilol within the first 24 hours.
  - B. Give 5 mg of intravenous metoprolol at the bedside.
  - C. Give 50 mg of oral metoprolol succinate at discharge.
  - D. Give no  $\beta$ -blocker at this time.
5. A 60-year-old man (weight 75 kg) presents to the ED with crushing substernal chest pain and ST-segment elevations on ECG. He has a medical history of diabetes and a 40 pack-year history of smoking. He is taken immediately to the catheterization laboratory for primary PCI, and a drug-eluting stent is placed in his left anterior descending artery. In addition to aspirin, which regimen would best maintain this patient's stent patency?
  - A. Clopidogrel 300-mg LD, followed by 75 mg daily for 12 months.
  - B. Prasugrel 60-mg LD, followed by 10 mg daily for 12 months.
  - C. Ticagrelor 180-mg LD, followed by 90 mg daily for 6 months.
  - D. Clopidogrel 600-mg LD, followed by 75 mg daily for 6 months.
6. A 60-year-old woman with New York Heart Association (NYHA) class IV heart failure (HF) (heart failure with reduced ejection fraction [HFrEF]) is admitted for increased shortness of breath and dyspnea at rest. Her extremities appear

- well perfused, but she has 3+ pitting edema in her lower extremities. Her vital signs include blood pressure 125/70 mm Hg, heart rate 92 beats/minute, and oxygen saturation (Sao<sub>2</sub>) 89% on 100% facemask. After initiating an intravenous diuretic, which intravenous agent is best to rapidly treat this patient's pulmonary symptoms?
- A. Dobutamine.
  - B. Milrinone.
  - C. Nitroglycerin.
  - D. Metoprolol.
7. A 75-year-old woman admitted for pneumonia has a history of several non-ST-segment elevation myocardial infarctions (NSTEMIs). She had an episode of sustained ventricular tachycardia (VT) during this hospitalization. Her corrected QT (QTc) interval was 380 milliseconds on the telemetry. Her left ventricular ejection fraction (LVEF) was found to be 25%. Her serum potassium and magnesium were 4.6 mEq/L and 2.2 mg/dL, respectively. Which intravenous agent is most appropriate for this patient's ventricular arrhythmias?
- A. Procainamide.
  - B. Metoprolol.
  - C. Magnesium.
  - D. Amiodarone.
8. A 53-year-old woman is admitted to the hospital after the worst headache she has ever had. Her medical history includes exertional asthma, poorly controlled hypertension, glaucoma, and hyperlipidemia. She is nonadherent to her medications and has not taken her prescribed blood pressure medications for 4 days. Vital signs include blood pressure 220/100 mm Hg and heart rate 65 beats/minute. She has retinal hemorrhaging on funduscopic examination. Which is most appropriate for this patient's hypertensive emergency?
- A. Fenoldopam 0.1 mcg/kg/minute.
  - B. Nicardipine 5 mg/hour.
  - C. Labetalol 0.5 mg/minute.
  - D. Enalaprilat 0.625 mg intravenously every 6 hours.
9. A 52-year-old woman has a witnessed cardiac arrest in a shopping mall and is resuscitated with an automatic external defibrillator device. On electrophysiologic study, she has inducible VT. Which is most appropriate for reducing the secondary incidence of sudden cardiac death (SCD)?
- A. Propafenone.
  - B. Amiodarone.
  - C. Implantable cardioverter-defibrillator (ICD).
  - D. Metoprolol.
10. The Sudden Cardiac Death in Heart Failure trial evaluated the efficacy of amiodarone or an ICD versus placebo in preventing all-cause mortality in ischemic and nonischemic patients with NYHA class II and III HF. There was a 7.2% absolute risk reduction and a 23% relative risk reduction in all-cause mortality at 60 months with an ICD versus placebo. Which best shows the number of patients needed to treat with an ICD to prevent one death versus placebo?
- A. 1.
  - B. 4.
  - C. 14.
  - D. 43.
11. You are working on a review article about newer treatment strategies for hypertensive crises. You want to ensure that you retrieve all relevant clinical trials and related articles on your subject. Which comprehensive database is most appropriate to search to ensure that you have not missed key articles?
- A. International Pharmaceutical Abstracts.
  - B. Iowa Drug Information Service.
  - C. Clin-Alert.
  - D. Excerpta Medica.
12. A physician on your team asks that you report an adverse drug reaction (ADR) experienced by a patient taking nitroprusside. The patient had severe hypotension after the initial bolus dose of nitroprusside, though his blood pressure was in the normal range before therapy initiation. The hypotension led to reduced renal perfusion, resulting in

oliguric acute kidney injury and subsequent hemodialysis. The patient had no known renal insufficiency before developing this complication. Which statement best describes The Joint Commission requirements for institutional ADR reporting?

- A. A MedWatch form must be completed that explains the situation in which the ADR occurred.
  - B. Institutions must create their own definition of ADR with which practitioners will be familiar.
  - C. Hospital staff members must use the Naranjo algorithm to assess the severity of the ADR.
  - D. Only severe or life-threatening ADRs need to be reported.
13. Your pharmacy and therapeutics committee wants you to do a pharmacoeconomic analysis of a new drug available to treat decompensated HF. This drug has a unique mechanism of action. Unlike other available inotropic therapies that can increase mortality, this drug appears to reduce long-term mortality. However, its cost is 10-fold greater than other available drugs. Which pharmacoeconomic analysis would best determine whether this new drug is a better formulary choice than the currently available agents?
- A. Cost-minimization.
  - B. Cost-effectiveness.
  - C. Cost-benefit.
  - D. Cost-utility.

***BPS Pharmacotherapy Specialty Examination Content Outline***

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-centered pharmacotherapy
  - a. Task 1: Knowledge statements: a–c, e, f, h, j–l, p
  - b. Task 2: Knowledge statements: a–d
  - c. Task 3: Knowledge statements: a–e
2. Domain 2: Drug Information and Evidence-Based Medicine
  - a. Task 1: Knowledge statements: a, e, g
  - b. Task 2: Knowledge statements: a, c, d, e, f, g, h, i
3. Domain 3: System-Based Standards and Population-Based Pharmacotherapy. Task 3: Knowledge statement: d

***Systems and Patient Care Problems***

In addition, this chapter covers the following systems and patient care problems:

1. Acute coronary syndrome
2. Acute decompensated heart failure
3. Adult cardiac arrest
4. Advanced cardiac life support
5. Basic life support and cardiopulmonary resuscitation
6. Life-threatening arrhythmias
7. Hypertensive crises (urgency and emergency)



## I. ACUTE CORONARY SYNDROME

### A. Definitions

1. Acute coronary syndrome (ACS) is a spectrum of conditions compatible with acute myocardial ischemia or infarction caused by an abrupt reduction in coronary blood flow (Figure 1).
2. This chapter will focus on the most common presentation of ACS (type 1 MI), as defined by the Fourth Universal Definition of Myocardial Infarction, which is caused by coronary thrombosis.
3. Atherogenic plaque rupture is the underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation leading to partial or total occlusion of the coronary artery.
4. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS).
  - a. STEMI
    - i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
    - ii. STEMI is an indication for immediate coronary angiography to determine whether reperfusion can be done (see section C in this section, “Decision for Invasive Management”).
  - b. NSTEMI-ACS
    - i. Suggested by the absence of persistent ST-segment elevation on ECG
    - ii. NSTEMI-ACS can be divided into unstable angina (UA) and NSTEMI according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in risk and severity.
    - iii. ECG abnormalities and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
    - iv. Optimal inhibition of thrombosis is paramount in ACS management.

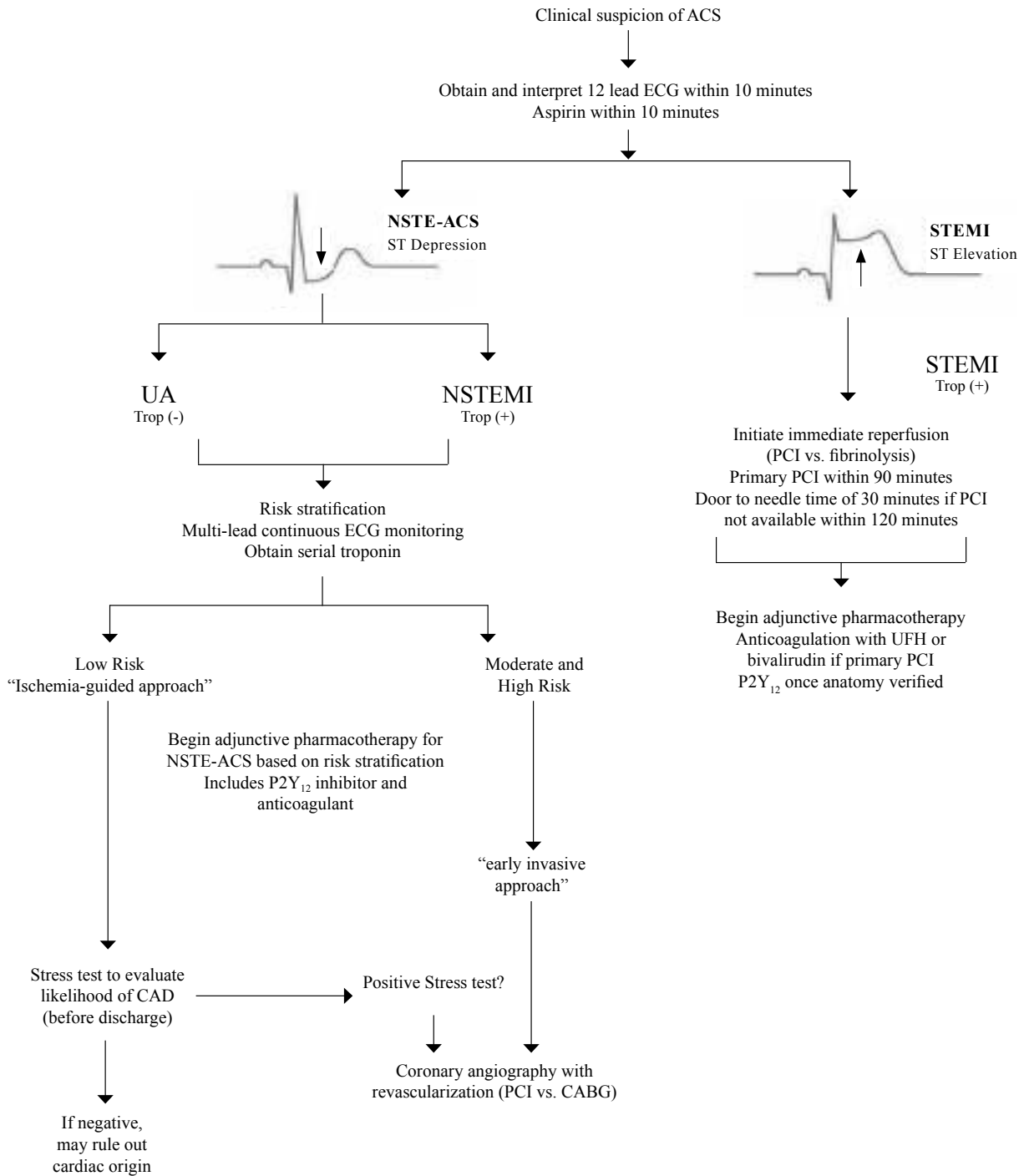
### B. Clinical Assessment and Initial Evaluation

1. A 12-lead ECG should be done and interpreted within 10 minutes of presentation.
  - a. Persistent ST-segment elevation should be treated according to the STEMI guidelines.
  - b. Serial ECGs can be done if the initial ECG is nondiagnostic.
2. Serial cardiac troponins should be obtained at presentation and 3–6 hours after symptom onset.
3. At initial presentation, the clinical history, angina symptoms and equivalents, physical assessment, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, anti-thrombotic therapies, and invasive management. Risk calculators include the following:
  - a. Thrombolysis in myocardial infarction (TIMI) risk score (available at [www.timi.org](http://www.timi.org) [accessed September 1, 2018]) is useful in predicting 30-day and 1-year mortality in patients with NSTEMI-ACS.
    - i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST deviation on ECG, two or more anginal events in previous 24 hours, aspirin use in previous 7 days, and elevated cardiac biomarkers
    - ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
    - iii. Patients with higher risk scores (e.g., TIMI of 3 or more) have a greater benefit from therapies such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and invasive strategies.
  - b. The Global Registry of Acute Coronary Events (GRACE) risk model ([https://www.outcomes-umasmed.org/grace/acs\\_risk2/index.html](https://www.outcomes-umasmed.org/grace/acs_risk2/index.html)) predicts in-hospital and postdischarge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.

**Table 1.** ACS Definition

	<b>Subjective Findings</b>	<b>Objective Findings</b>	<b>Extent of Injury</b>
NSTE-ACS UA	<p>Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion</p> <p>Pain usually starts in the retrosternal area and can radiate to either or both arms, neck, or jaw</p> <p>Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope</p> <p>Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent</p> <p>Less common atypical symptoms<sup>a</sup> (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope</p>	<p>ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur</p> <p>No positive biomarkers for cardiac necrosis</p>	No myocardial injury; partial occlusion of coronary artery
NSTEMI		<p>ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur</p> <p>Positive biomarkers (troponin I or T elevation)</p>	Myocardial injury; partial occlusion of coronary artery
STEMI	Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation	<p>ST-segment elevation &gt; 1 mm above baseline on ECG in two or more contiguous leads</p> <p>Positive biomarkers (troponin I or T elevation)</p>	Myocardial necrosis; total occlusion of coronary artery

<sup>a</sup>Up to one-half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort.



**Figure 1.** Acute coronary syndrome diagnosis and risk stratification.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

**C. Decision for Invasive Management****1. STEMI**

- a. The goal of therapy is to restore the patency of the infarct-related artery and minimize the infarct size. Secondary goals include preventing complications such as arrhythmias or death as well as controlling chest pain and associated symptoms.
- b. Requires urgent revascularization either interventionally or with drug therapy (i.e., fibrinolysis)
- c. Primary PCI is preferred to lytic therapy. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
- d. Fibrinolytic therapy is indicated for patients with a STEMI in whom PCI cannot be done (discussed later in chapter). If PCI cannot be done within 120 minutes, performance measure for lytic administration includes a door-to-needle time of 30 minutes.

**2. NSTEMI-ACS**

- a. The goal of therapy is to prevent total occlusion of the related artery and to control chest pain and associated symptoms. Patients with NSTEMI-ACS are treated on the basis of risk (TIMI, GRACE) with either an early invasive strategy (interventional approach) or an ischemia-guided strategy (a conservative management strategy using medications rather than an interventional approach).
- b. Early invasive strategy is a diagnostic angiography with intent to do revascularization, if appropriate, depending on coronary anatomy.
  - i. Indicated in those with NSTEMI-ACS who have refractory angina or hemodynamic or electrical instability or those with high risk on the basis of clinical findings
  - ii. Routine invasive therapy is generally superior to an ischemia-guided strategy (results in lower rates of recurrent UA, recurrent hospitalization, MI, and death) in patients with one or more of the following risk features: advanced age (older than 70), previous MI or revascularization, ST deviation, HF, depressed resting left ventricle (LV) function (i.e., LVEF less than 40%), noninvasive stress findings, high TIMI or GRACE scores, markedly elevated troponins, and diabetes.
  - iii. Not for those with serious comorbidities or contraindications to such procedures (hepatic, renal, pulmonary failure, cancer), for whom the risks for the procedure may outweigh the benefits of revascularization
- c. Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients have refractory or recurrent ischemic symptoms or develop hemodynamic instability.
  - i. Recommended for patients with a low risk score (TIMI 0 or 1, GRACE less than 109)
  - ii. Indicated for those with acute chest pain with a low likelihood of ACS who are troponin negative (preferred for low-risk women)
  - iii. Can be chosen according to clinician and patient preference
3. Patients should receive anti-ischemic and analgesic medications early in care: morphine, oxygen, nitroglycerin, and aspirin plus a  $\beta$ -blocker (Table 2).

**Table 2.** Initial Anti-ischemic and Analgesic Therapies for ACS

Therapy	Comments
M = Morphine or other narcotic analgesic	<p>Provides analgesia and decreased pain-induced sympathetic/adrenergic tone</p> <p>Commonly used because it can also induce vasodilation and mediate some degree of preload and afterload reduction</p> <p>Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications<sup>a</sup></p> <p>Carries a class IIb recommendation, given that at least two large trials have identified an association between morphine administration and risk of death<sup>b</sup></p> <p>Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease area under the curve</p>
O = Oxygen	<p>Can help attenuate anginal pain secondary to tissue hypoxia</p> <p>Consider supplemental oxygen if <math>\text{SaO}_2 &lt; 90\%</math>, respiratory distress, or high-risk features of hypoxemia<sup>c</sup></p> <p>Excessive supplemental oxygen without depressed <math>\text{SaO}_2</math> can be associated with increased morbidity and mortality</p>
N = Nitroglycerin	<p>Facilitates coronary vasodilation and may also be helpful in severe cardiogenic pulmonary edema caused by venous capacitance</p> <p>NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 9-1-1); afterward, assess need for IV administration</p> <p>IV administration used in first 48 hr for persistent ischemic chest pain, HF, and HTN</p> <p>IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min</p> <p>Use should not preclude other mortality-reducing therapies (<math>\beta</math>-blocker, ACE inhibitor)</p> <p>Contraindications: Sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); SBP &lt; 90 mm Hg or <math>\geq 30</math> mm Hg below baseline, HR &lt; 50 beats/min, HR &gt; 100 beats/min in absence of symptomatic HF; right ventricular infarction</p>
A = Aspirin	<p>Inhibits platelet activation</p> <p>Mortality-reducing therapy</p> <p>Chew and swallow non-enteric coated aspirin 162–325 mg <math>\times</math> 1 dose<sup>c</sup></p> <p>Clopidogrel if aspirin allergy</p> <p>Performance measure</p>
$\beta$ -Blocker	<p>Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias and increase long-term survival</p> <p>Oral <math>\beta</math>-blocker<sup>c</sup> should be initiated within 24 hr in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to <math>\beta</math>-blockade (e.g., PR interval &gt; 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease)</p> <p>Reasonable to continue in patients with NSTEMI-ACS with normal LV function<sup>a</sup></p> <p>Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF<sup>c</sup>; add cautiously in decompensated HF</p> <p>Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol, penbutolol)</p> <p>IV <math>\beta</math>-blocker<sup>d</sup> is potentially harmful in patients with risk factors for shock (age &gt; 70 yr, HR &gt; 110 beats/min, SBP &lt; 120 mm Hg, and late presentation)</p>

<sup>a</sup>Class IIb may be considered.

<sup>b</sup>From: Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;371:1016-27; and Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* 2005;149:1043-9.

<sup>c</sup>Class I = should be performed or administered; class IIa = reasonable to be performed or administered.

<sup>d</sup>Class III = not to be administered or harmful.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; HTN = hypertension; LV = left ventricle; NTG = nitroglycerin; SBP = systolic blood pressure.

4. Patients with STEMI and NSTEMI-ACS should be treated with antiplatelet and anticoagulant therapy (Tables 3–9).
  - a. Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
  - b. Combination therapy with several antiplatelet agents plus a concomitant anticoagulant is the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
  - c. The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 3).
  - d. In general, all patients receive aspirin and P2Y<sub>12</sub> receptor antagonists, and a minority of patients may benefit from the addition of GP IIb/IIIa inhibition in the acute management of ACS.

**Table 3.** Antiplatelet Management Strategies According to ACS Presentation

Antiplatelet Agent	NSTEMI-ACS Ischemia Guided	NSTEMI-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
P2Y <sub>12</sub> receptor antagonist	Clopidogrel TIC	Clopidogrel PRA <sup>a</sup> TIC <sup>a</sup>	Clopidogrel PRA TIC	Clopidogrel <sup>b</sup>
GP IIb/IIIa inhibitor	Greatest benefit when given to patients with high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or TIC <sup>c</sup>			

<sup>a</sup>It may be reasonable to choose TIC or PRA (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTEMI-ACS (class IIa, 2014 NSTEMI-ACS guideline).

<sup>b</sup>Pre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

<sup>c</sup>Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with P2Y<sub>12</sub> inhibitor. It is reasonable (class IIa, 2014 NSTEMI-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTEMI-ACS treated with UFH and adequately pretreated with clopidogrel.

PCI = percutaneous coronary intervention; PRA = prasugrel; TIC = ticagrelor.

e. Antiplatelet recommendations

i. Aspirin

- (a) An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A<sub>2</sub>—and thromboxane A<sub>2</sub>—mediated platelet activation
- (b) Given to all patients (class I)
- (c) Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
- (d) LD is necessary for aspirin-naïve patients; avoid enteric coated initially because of delayed and reduced absorption.
  - (1) Dosing is 162–325 mg for patients at initial presentation of ACS (Table 4).
  - (2) Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
- (e) Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
  - (1) High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).
  - (2) High doses (greater than 160 mg) have not been shown to improve outcomes after ACS more effectively than lower doses (less than 160 mg).

- (f) Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y<sub>12</sub> receptor inhibitor is indicated for all patients after ACS for at least 12 months (see D, “Long-term Management After ACS”). The optimal aspirin dose in patients treated with DAPT appears to be 75–100 mg daily.

**Table 4.** Guideline Recommendations for Aspirin Therapy in ACS with or without PCI<sup>a</sup>

Guideline Recommendation	Class/Grade
Initiate 162–325 mg of ASA before PCI; after PCI, give ASA indefinitely • 2013 ACCF/AHA guideline for STEMI	I
Initiate 81–325 mg of non–enteric-coated ASA before PCI in patients already taking ASA; in patients not taking ASA, give 325 before PCI; after PCI, continue ASA indefinitely • 2014 NSTE-ACS guideline • 2011 ACCF/AHA/SCAI guideline for PCI	I
81 mg of ASA preferred to higher maintenance doses • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI • 2011 ACCF/AHA/SCAI guideline for PCI	Ila Ila Ila

<sup>a</sup>Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ASA = acetylsalicylic acid; SCAI = Society for Cardiovascular Angiography and Interventions.

ii. P2Y<sub>12</sub> inhibitors

- (a) Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation
- (b) P2Y<sub>12</sub> inhibitor therapy is given to all patients (class I).
- (c) Choice of oral P2Y<sub>12</sub> inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences (Tables 5–7).
  - (1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).
  - (2) The efficacy of ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).
- (d) Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy (Table 5).
- (e) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).
  - (1) It is reasonable to choose ticagrelor over clopidogrel for P2Y<sub>12</sub> inhibition in patients with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).
  - (2) It is reasonable to choose prasugrel over clopidogrel for P2Y<sub>12</sub> inhibition in patients with NSTE-ACS or STEMI who undergo PCI and who are not at high risk of bleeding complications and have no history of transient ischemic attack or stroke (class IIa).
  - (3) Although not yet included in guidelines, results of the first head-to-head ISAR-REACT 5 open-label trial showed that prasugrel was superior to ticagrelor in reducing ischemic end points (6.9% vs. 9.3%,  $p=0.0006$ ) without increasing bleeding risk in 4018 patients with ACS undergoing PCI; however, limitations to this study have been identified.
- (f) Limited data are available on the long-term safety or efficacy of “switching” patients treated for weeks or months with a P2Y<sub>12</sub> inhibitor to a different P2Y<sub>12</sub> inhibitor.

**Table 5.** Guideline Recommendations for P2Y<sub>12</sub> Inhibitor Therapy in ACS with or without PCI

Guideline Recommendation	Class/Grade <sup>a</sup>
An LD of P2Y <sub>12</sub> receptor inhibitor should be given before PCI. Options include: a. Clopidogrel <sup>b</sup> 600 mg followed by 75 mg daily; b. PRA 60 mg followed by 10 mg daily; or c. TIC 180 mg followed by 90 mg BID • 2013 ACCF/AHA guideline for STEMI • 2014 NSTE-ACS guideline	I LOE B LOE B LOE B
For patients with NSTE-ACS treated with an early invasive or ischemia-guided strategy: a. Clopidogrel 600 mg followed by 75 mg daily b. TIC 180 mg followed by 90 mg BID • 2014 NSTE-ACS guideline	I LOE B LOE B
For patients with NSTE-ACS treated with an early invasive or ischemia-guided strategy: It is reasonable to use TIC in preference to clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
For patients with NSTE-ACS treated with PCI who are not at risk of bleeding complications: • It is reasonable to choose PRA over clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
PRA should not be administered to patients with a history of TIA or stroke • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI	Class III

<sup>a</sup>Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

<sup>b</sup>Before PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

BID = twice daily; LOE = level of evidence; TIA = transient ischemic attack.

**Table 6.** Comparison of Oral P2Y<sub>12</sub> Receptor Inhibitors

Parameter	Clopidogrel (Plavix) <sup>a</sup>	Prasugrel (Effient) <sup>b</sup>	Ticagrelor (Brilinta) <sup>c</sup>
Mechanism of action	Thienopyridine; inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor	Thienopyridine; inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor	Inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor
Peak platelet inhibition	300-mg LD ~6 hr 600-mg LD ~2 hr	60-mg LD ~30 min <sup>d</sup>	180 mg LD ~30 min <sup>d</sup>
% Platelet inhibition	30%–40%	60%–70%	60%–70%
LD	300–600 mg <sup>e</sup>	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily; (5 mg if < 60 kg, BW ≥ 75 yr) <sup>f</sup>	90 mg BID <sup>g</sup>
Metabolism	Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes	Prodrug; converted by one step to active metabolite by several CYP pathways	Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor
Reversible platelet binding	No	No	Yes
Half-life	8 hr (metabolite)	3.7 hr (metabolite, range 2–15 hr)	7 hr (parent), 9 hr (active metabolite)
Nonresponders	Exposure to active drug affected by <i>CYP2C19</i> genetic polymorphisms	No known issues	No known issues



**Table 6.** Comparison of Oral P2Y<sub>12</sub> Receptor Inhibitors (*Cont'd*)

Parameter	Clopidogrel (Plavix) <sup>a</sup>	Prasugrel (Effient) <sup>b</sup>	Ticagrelor (Brilinta) <sup>c</sup>
Drug-drug interactions, drug-disease interactions, and common nonbleeding-related AEs	PPIs inhibit <i>CYP2C19</i> (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs	No clinically significant drug interactions; more bleeding with NSAIDs, OACs	Careful with asthma owing to dyspnea (up to 15%) and bradycardia (can cause ventricular pauses); More bleeding with NSAIDs, OACs Strong 3A4 inhibitors increase TIC concentrations; strong 3A4 inducers decrease TIC concentrations; do not exceed 40 mg of simvastatin or lovastatin Limit aspirin to < 100 mg; monitor digoxin concentrations
Surgery hold time <sup>h</sup>	5 days	7 days	5 days
Bleeding risk	Less than PRA and TIC with standard dosing	Risk of non-CABG, spontaneous, and fatal bleeds higher than with standard-dose clopidogrel	Risk of non-CABG bleeds higher than with standard-dose clopidogrel
Box warning	<i>CYP2C19</i> polymorphisms	Age-related bleeding; CVA/TIA	Aspirin dosing > 100 mg
Contraindications	Active bleeding	Active bleeding; TIA, CVA	Active bleeding; ICH; severe hepatic disease
Supporting trials	CREDO, CURE, PCI-CURE, CLARITY, COMMIT	TRITON-TIMI 38, TRILOGY	PLATO, PEGASUS
FDA indication	ACS managed medically or with PCI	ACS with PCI	ACS managed medically or with PCI

<sup>a</sup>Administer clopidogrel indefinitely if aspirin allergy. Avoid LD if patient is ≥ 75 yr in STEMI when fibrinolysis is given.

<sup>b</sup>Avoid PRA in patients with active pathologic bleeding or a history of TIA or CVA and in patients > 75 yr unless the patient has diabetes mellitus or a history of MI.

<sup>c</sup>Avoid TIC in patients with active pathologic bleeding or a history of ICH. Avoid aspirin doses > 100 mg daily (exception: first dose of 325 mg).

<sup>d</sup>A significant antiplatelet effect has been observed at 30 min. Onset of effect is quicker, and extent of platelet inhibition is greater than with clopidogrel.

<sup>e</sup>A 600-mg LD results in greater, more rapid, and more reliable platelet inhibition than a 300-mg LD.

<sup>f</sup>Although 5 mg in patients weighing < 60 kg should be considered, this dose has not been studied in patients undergoing PCI.

<sup>g</sup>Maintenance dosing of 60 mg BID is FDA approved for reducing thrombotic events after an initial 12 mo of therapy.

<sup>h</sup>In emergency CABG, clopidogrel and TIC should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ADP = adenosine diphosphate; AE = adverse event; BW = boxed warning; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; P-gp = P-glycoprotein; PPI = proton pump inhibitor; TIA = transient ischemic attack.

## ii. Intravenous P2Y<sub>12</sub> inhibitor

- Cangrelor, a direct-acting, rapidly reversible, intravenous P2Y<sub>12</sub> inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30-mcg/kg intravenous bolus followed by a 4-mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.
- Rapid onset and offset (half-life less than 5 minutes) allows a quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.
- Primarily studied in the setting of PCI only and may be considered in those who are not candidates for oral agents

- (d) Pivotal trials comparing cangrelor with clopidogrel in ACS have not shown the superiority of cangrelor; however, both the CHAMPION PHOENIX PCI and the PLATFORM trials were discontinued prematurely.
  - (e) Cangrelor had better efficacy than post-PCI clopidogrel with increases in minor bleeding (not major) (CHAMPION PHOENIX).
  - (f) Cangrelor treatment is associated with a risk of dyspnea.
  - (g) Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
  - (h) Cangrelor has a potential use as a bridge therapy after discontinuation of oral P2Y<sub>12</sub> inhibitors in high-risk patients undergoing coronary artery bypass grafting (CABG) (JAMA 2012;307:265-74).
  - (i) The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the P2Y<sub>12</sub> and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor.
  - (j) Expense and lack of evidence showing superiority to other P2Y<sub>12</sub> inhibitors limit cangrelor's use.
  - (k) Cangrelor has not been included in the ACS guidelines to date because FDA approval occurred after guideline release.
- iv. Intravenous GP IIb/IIIa inhibitors
- (a) Intravenous GP IIb/IIIa receptor inhibitors can be added to aspirin with or without an oral P2Y<sub>12</sub> inhibitor for cardiovascular (CV) benefit in select high-risk patients in the acute management of ACS.
  - (b) Block the final common pathway of platelet aggregation; achieve 80% inhibition of ex vivo platelet aggregation
  - (c) GP IIb/IIIa inhibition may be beneficial in patients with high-risk features, particularly in those inadequately pretreated with P2Y<sub>12</sub> inhibition.
  - (d) Double-bolus eptifibatide and high-dose bolus tirofiban are class I options for the invasive strategy (Table 7).
  - (e) GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through decreasing documented MIs, but can increase the risk of bleeding.
  - (f) Most, but not all, data were gathered in the era before routine P2Y<sub>12</sub> inhibitor use.
  - (g) Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (elevated biomarkers, diabetes, undergoing revascularization) and in those not receiving adequate pretreatment with clopidogrel or ticagrelor.
  - (h) It is reasonable (class IIa, 2014 NSTEMI-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTEMI-ACS treated with UFH and adequately pretreated with clopidogrel or ticagrelor.
  - (i) Most studies combined GP IIb/IIIa inhibitors with UFH as the anticoagulant.
  - (j) Upstream administration (given before PCI) has not been shown superior to delayed administration (given at time of PCI).
    - (1) Upstream administration is noninferior to delayed timing for reducing ischemic events.
    - (2) Significantly higher bleeding rates occur in those receiving upstream GP IIb/IIIa inhibitors than in those receiving delayed administration.
    - (3) Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice but not in the practice guidelines.

## (k) Common adverse events of GP IIb/IIIa inhibitors:

- (1) Most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
- (2) Note that the smaller-molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease the risk of bleeding; monitor SCr (CrCl).
- (3) All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and Plt. When administered with UFH, rates of thrombocytopenia with either tirofiban or eptifibatide are no greater than with UFH alone.
- (4) Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion and are preferred (class IIb) in the NSTEMI-ACS guideline.

**Table 7.** GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI<sup>a,b</sup>

Agent	Dosing	Renal Adjustments
Eptifibatide (Integrilin)	PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr <sup>c</sup> ; ACS without PCI: Of uncertain benefit in patients adequately pretreated with a P2Y <sub>12</sub> receptor inhibitor; single bolus used as above	If CrCl < 50 mL/min, reduce infusion by 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr	If CrCl ≤ 60 mL/min, reduce infusion by 50%

<sup>a</sup>Adding GP IIb/IIIa inhibitors to aspirin therapy is most beneficial in patients with high-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with P2Y<sub>12</sub> inhibitors. Administration of GP IIb/IIIa inhibitors to patients adequately treated with P2Y<sub>12</sub> inhibitors is of uncertain clinical benefit.

<sup>b</sup>GP IIb/IIIa inhibitors should be used in combination with heparin (either UFH or low-molecular-weight heparin) or used provisionally with bivalirudin.

<sup>c</sup>Double bolus is recommended to support PCI in STEMI and NSTEMI-ACS.

IVB = intravenous bolus.

## v. Platelet function testing

- (a) Although platelet function can be evaluated by platelet function testing or genotyping, neither is routinely done in the clinical setting.
- (b) Although platelet function and genetic testing are not routine and have not been endorsed by guidelines to date, several clinical trials have offered promise with utilizing genetic information in order to optimize antiplatelet choice and outcomes.

- f. Anticoagulant recommendations
  - i. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9), irrespective of initial treatment strategy.
  - ii. Use of anticoagulants is typically concentrated in the procedural setting, though use may continue for a finite period after the procedure.
  - iii. Selection and use among agents may depend on ACS presentation, timing or dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding during procedure.
  - iv. Anticoagulants increase the risk of bleeding and will require some type of monitoring for agent-specific risks.

**Table 8.** Anticoagulant Management Strategies in ACS

Management Strategy	Class I Recommendations <sup>a</sup>
STEMI (PPCI)	UFH, bivalirudin
STEMI, with fibrinolytic <sup>b</sup> therapy	UFH, enoxaparin, fondaparinux
NSTE-ACS, early invasive strategy	Enoxaparin, bivalirudin, <sup>c</sup> UFH
NSTE-ACS, ischemia-guided strategy	Enoxaparin, fondaparinux, <sup>d</sup> UFH

<sup>a</sup>Class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

<sup>b</sup>Fibrinolytics preferred when PCI cannot be done within 120 min of first medical contact (class I). Door-to-needle time goal < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with IV UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

<sup>c</sup>If bleeding risk is high, it is reasonable to use bivalirudin monotherapy in preference to UFH plus GP IIb/IIIa inhibitor (class IIa).

<sup>d</sup>Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class I recommendation in the 2014 NSTE-ACS guidelines (for an ischemia-guided strategy) and a class III or harmful recommendation in the 2011 PCI and 2013 STEMI guidelines when PCI is indicated.

PPCI = primary percutaneous coronary intervention; SC = subcutaneous(ly).

- g. Anticoagulant agents
  - i. UFH
    - (a) Exerts its effects as an indirect thrombin inhibitor on fibrin-bound clots
    - (b) Given as an intravenous bolus with or without infusion and adjusted according to activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to maintain therapeutic anticoagulation according to specific hospital protocol, usually continued for 48 hours or until PCI
      - (1) Intravenous UFH: Initial bolus of 60 units/kg (maximum 4000 units)
      - (2) Initial infusion of 12 units/kg/hour (maximum 1000 units/hour)
    - (c) Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
    - (d) Monitoring includes aPTT or ACT, Hgb/Hct, and Plt.
    - (e) Unlike other anticoagulants, UFH is not renally cleared and can be used safely in those with renal impairment.
  - ii. Enoxaparin: Molecular weight is one-third of UFH with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.
    - (a) Given as subcutaneous injection at least 2 inches on either side of the navel at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternate dosing sites
      - (1) Dosing varies depending on the reperfusion strategy and the time from the last dose to the procedure (Table 9).
      - (2) 30-mg intravenous bolus given in STEMI (if age younger than 75) and in select patients with NSTE-ACS

- (3) Specific periprocedural dosing for PCI in relation to time of last subcutaneous dose (Table 9)
    - (4) Decrease dosing interval to once daily when CrCl is less than 30 mL/minute.
  - (b) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl for dosing; monitor Hgb, Hct, Plt
  - (c) Risks include bleeding, injection site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT with or without thrombosis, mechanical prosthetic valve thrombosis (in pregnancy)
- iii. Fondaparinux
  - (a) Selective inhibitor of activated factor X
  - (b) Longest half-life of anticoagulants (17 hours)
  - (c) Given as a subcutaneous injection into fatty tissue at a 90-degree angle into a pinched skinfold; alternate dosing sites between the left and right anterolateral and posterolateral abdominal wall
    - (1) Dosing NSTEMI-ACS: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI
    - (2) Not to be used as the sole anticoagulant during PCI (class III)
    - (3) Contraindicated if CrCl is less than 30 mL/minute
  - (d) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindication; monitor Hgb, Hct, Plt
  - (e) Risks include bleeding, thrombocytopenia, and spinal or epidural hematomas.
  - (f) No increased risk of HIT
- iv. Bivalirudin
  - (a) A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and inhibits thrombin-mediated platelet aggregation
  - (b) Given as an intravenous bolus with fixed-rate infusion and usually continued until the end of PCI (with or without delay after infusion in some high-risk patients)
    - (1) Early invasive strategy dosing: 0.1-mg/kg LD followed by 0.25 mg/kg per hour (only in patients with planned PCI), continued until diagnostic angiography or PCI
    - (2) PCI dosing: 0.75-mg/kg intravenous bolus, 1.75 mg/kg/hour intravenously continued throughout the procedure
    - (3) Adjust the infusion rate to 1 mg/kg/hour when the CrCl is less than 30 mL/minute or to 0.25 mg/kg/hour in patients receiving hemodialysis.
    - (4) Can extend duration of infusion for up to 4 hours after procedure for prolonged antiplatelet protection
  - (c) Does not require monitoring for adjustment during PCI; monitor SCr (adjustment required for infusion only in those with impaired CrCl), Hgb, Hct, Plt
  - (d) Can be given in patients with history of or suspected HIT undergoing PCI
- h. Guideline recommendations for specific anticoagulants
  - i. In an **ischemia-guided strategy**, UFH, enoxaparin, and fondaparinux are class I recommended options.
  - ii. In an **invasive strategy**, UFH, enoxaparin, and bivalirudin are class I recommended options.
    - (a) Fondaparinux should not be used as the sole anticoagulant to support PCI (class III). An additional 85 units/kg of intravenous UFH is required immediately before PCI revascularization to reduce the risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used; re-bolus as needed according to target ACT.
    - (b) Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy.

- (1) An additional dose of 0.3 mg/kg of intravenous enoxaparin should be administered at the time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or who received the last subcutaneous dose 8–12 hours before PCI.
  - (2) Patients who have received enoxaparin within 8 hours of the last subcutaneous dose generally have adequate anticoagulation to undergo PCI without supplemental bolus.
  - (3) Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).
  - (c) In those at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (class IIa).
    - (1) For patients who have received UFH, wait 30 minutes and then give a 0.75-mg/kg intravenous LD, followed by a 1.75-mg/kg/hour intravenous infusion.
    - (2) For patients already receiving a bivalirudin infusion, give an additional 0.5-mg/kg LD, and increase the infusion to 1.75 mg/kg/hour during PCI.
  - (d) Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.
- iii. In patients undergoing **primary PCI**, either UFH or bivalirudin is preferred.

**Table 9.** Antithrombotic Dosing in ACS with or without PCI

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	—	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
NSTE-ACS	60 units/kg IVB (max 4000 units), 12 units/kg/hr IV (max 1000 units/hr) for 48 hr or until PCI; goal aPTT/anti-Xa according to hospital-specific protocol	1 mg/kg SC every 12 hr for 24–48 hr or until PCI or throughout hospitalization (up to 8 days); 30 mg IVB	2.5 mg SC daily	0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy)
PCI	Supplemental doses to target ACT <sup>a</sup> ; if GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB; if no GP IIb IIIa inhibitors, UFH 70–100 units/kg IVB	If last dose < 8 hr, nothing additional needed; if last dose > 8 hr, 0.3 mg/kg IVB if last dose 8–12 hr before or < 2 therapeutic doses received before PCI	Fondaparinux should not be used as a sole anticoagulant for PCI	0.75 mg/kg IVB, 1.75mg/kg/hr IV d/c at end of PCI, or continue for up to 4 hr after procedure if needed; hold UFH 30 min before administration

**Table 9.** Antithrombotic Dosing in ACS with or without PCI (*Cont'd*)

	<b>Unfractionated Heparin</b>	<b>Enoxaparin (Lovenox)</b>	<b>Fondaparinux (Arixtra)</b>	<b>Bivalirudin (Angiomax)</b>
STEMI ± primary PCI	Supplemental doses to target ACT <sup>a</sup> ; if GP IIb/IIIa inhibitor, UFH 50–70 units/kg IVB; if no GP IIb/IIIa inhibitor, UFH 70–100 units/kg IVB	30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses; if > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses	2.5 mg IVB; then 2.5 mg SC daily <sup>b</sup>	0.75 mg/kg IVB, 1.75 mg/kg/hr IV
Dose adjustments and contraindications	Avoid if history of HIT	If CrCl < 30 mL/min, 1 mg/kg SC daily; avoid if history of HIT	Contraindicated if CrCl < 30 mL/min	Adjust infusion dose in severe renal dysfunction. If CrCl < 30 mL/min, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr

<sup>a</sup>Target ACT is 250–300 s for HemoTec and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

<sup>b</sup>Fondaparinux should not be used as the sole anticoagulant in PCI.

ACT = activated clotting time; HIT = heparin-induced thrombocytopenia; IVB = intravenous bolus; LMWH = low-molecular-weight heparin.

5. **Fibrinolytic therapy** is indicated for patients with a STEMI in whom PCI cannot be done (Table 10).
  - a. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with a STEMI (class I when onset of ischemic symptoms is within the previous 12 hours) when it is expected that primary PCI cannot be done within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
  - b. When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended.
  - c. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy after fibrinolysis for at least 48 hours with intravenous UFH or intravenous/subcutaneous enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or intravenous/subcutaneous fondaparinux during hospitalization, up to 8 days.
    - i. UFH administration of a 60-unit/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units/hour), to obtain an aPTT of 1.5–2.0 times control (about 50–70 seconds) for at least 48 hours
    - ii. Enoxaparin 30 mg intravenously (if 75 or older, omit bolus), followed in 15 minutes by a 1-mg/kg subcutaneous injection (if 75 or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute, extend dosing interval to daily administration.
    - iii. Fondaparinux administered with an initial 2.5-mg intravenous dose, followed in 24 hours by 2.5-mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute) for the duration of the index hospitalization, for up to 8 days, or until revascularization

**Table 10.** Fibrinolytic Therapy

	Dosing
Alteplase (t-PA, Activase)	$\leq 67$ kg: 15 mg IVP over 1–2 min, then 0.75 mg/kg IV over 30 min (max 50 mg), then 0.5 mg/kg (max 35 mg) over 60 min $> 67$ kg: 15 mg IVP over 1–2 min, then 50 mg over 30 min, then 35 mg over 1 hr (max total dose 100 mg)
Reteplase (r-PA, Retavase)	10 units IVP; repeat 10 units IV in 30 min
Tenecteplase (TNK-t-PA, TNKase)	$< 60$ kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; $\geq 90$ kg: 50 mg IVP ( $\sim 0.5$ mg/kg)

IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

**Table 11.** Contraindications to Fibrinolytic Therapy

Relative Contraindications	Absolute Contraindications
BP $> 180/110$ mm Hg on presentation or history of chronic poorly controlled HTN	Any prior hemorrhagic stroke
History of ischemic stroke $> 3$ mo before	Ischemic stroke within 3 mo (except in past 4½ hr)
Recent major surgery ( $< 3$ wk before)	Intracranial neoplasm or arteriovenous malformation
Traumatic or prolonged CPR ( $> 10$ min)	Active internal bleeding
Recent internal bleeding (within 2–4 wk)	Aortic dissection
Active peptic ulcer	Considerable facial trauma or closed-head trauma in past 3 mo
Noncompressible vascular punctures	Intracranial or intraspinal surgery within 2 mo
Pregnancy	Severe uncontrolled HTN (unresponsive to emergency therapy)
Known intracranial pathology (dementia)	For streptokinase, <sup>a</sup> treatment within previous 6 mo (if considering streptokinase again)
OAC therapy	

<sup>a</sup>Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CPR = cardiopulmonary resuscitation.

#### D. Long-term Management After ACS

##### 1. DAPT

- a. Given at least 12 months after ACS
- b. DAPT reduces mortality after ACS, regardless of whether the patient received stenting.
  - i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients after ACS (class I).
  - ii. In patients who were treated with an ischemia-guided therapy, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
  - iii. After PCI (bare metal stent or drug-eluting stent), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
- c. Early discontinuation of DAPT
  - i. Early discontinuation is reasonable when the risk of morbidity exceeds the expected benefit (class IIa).
    - (a) DAPT should be continued after ACS (with or without stent) for at least 12 months (class I).
    - (b) Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective stent placement (class I, 6 months duration for elective PCI).



- ii. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients with a higher ischemic risk and a lower bleeding risk.
- iii. Trials comparing shorter DAPT durations have evaluated newer-generation stents in all patients undergoing PCI (including elective cases).
- iv. Compared with first-generation stents, newer-generation stents have an improved safety profile and a lower risk of stent thrombosis.
- v. Proton pump inhibitors can reduce the risk of gastrointestinal (GI) bleeding from DAPT.
- d. Long-term DAPT
  - i. In general, longer-duration DAPT may be reasonable for patients at a higher ischemic risk with a lower bleeding risk.
  - ii. Trials evaluating the need for an extended DAPT duration (greater than 12 months) in patients with and without ACS undergoing PCI show a reduction in stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months.
  - iii. The risk of stent thrombosis is greater on DAPT cessation; however, continued DAPT beyond 1 year is not associated with reduced CV or total mortality.
  - iv. A longer duration of P2Y<sub>12</sub> inhibitor therapy is an individualized approach according to the patient's risk of ischemia and bleeding.
    - (a) DAPT may be reasonable beyond 12 months if the patient is at high risk and has no significant history of bleeding while receiving DAPT (class IIb).
    - (b) A DAPT score derived from the DAPT study may help in deciding whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).
      - (1) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as the P2Y<sub>12</sub> inhibitor
      - (2) For those with a high DAPT score (2 or greater), prolonged DAPT reduces net (ischemic plus bleeding) events.
      - (3) For those with a low DAPT score (less than 2), the benefit-risk ratio for prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events).
      - (4) Duration of DAPT for more or less than 12 months should jointly be made by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with the risks of bleeding.
  - v. Ticagrelor has been shown to reduce CV end points of death, MI, and revascularization to a greater extent than placebo at a reduced dose of 60 mg twice daily (after at least 12 months of 90 mg twice daily) with less bleeding than extended use of 90 mg twice daily (N Engl J Med 2015;372:1791-800).
- 2.  $\beta$ -Blockers
  - a. Indicated for all patients unless contraindicated
  - b. If not initiated orally within the first 24 hours, reevaluate for possible initiation before discharge.
  - c. Continue for at least 3 years (when EF is greater than 40%).
  - d. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with an EF less than 40%.
- 3. Angiotensin-converting enzyme (ACE) inhibitors
  - a. ACE inhibitors should be initiated and continued indefinitely for all patients with an LVEF of 40% or less and in those with hypertension, diabetes mellitus, or stable chronic kidney disease, unless contraindicated.
  - b. ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.
  - c. Angiotensin receptor blockers (ARBs) are indicated if the patient has contraindications to or is intolerant of ACE inhibitors.
  - d. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

**Table 12.** DAPT Score to Determine Favorability of Prolonged DAPT

Factors Used to Calculate DAPT Score	Add Points for Total Score <sup>a</sup>
Age $\geq 75$	-2
Age 65–74	-1
Current tobacco user	1
Diabetes mellitus	
NSTEMI or STEMI at presentation	
Prior MI or PCI	
Stent diameter $< 3$ mm	
Paclitaxel-eluting stent	
CHF or LVEF $< 30\%$	2
Saphenous vein graft PCI	2

<sup>a</sup>A score  $\geq 2$  favors prolonged DAPT; a score  $< 2$  is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction.

Information from: 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; and Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735-49.

4. Aldosterone receptor blockers
  - a. Indicated in patients who are already receiving an ACE inhibitor and  $\beta$ -blocker after MI and who have an LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated
  - b. Contraindications include hyperkalemia (potassium  $[K^+]$  5.0 or greater), CrCl less than 30 mL/minute, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
5. Lipid-lowering therapies
  - a. High-intensity statins are indicated in all patients after ACS without contraindication and are generally initiated as soon as possible within the first 24 hours.
  - b. In high-risk patients achieving a less-than-expected response to statins (less than a 50% reduction in low-density lipoprotein cholesterol [LDL]), or in those who are completely statin intolerant, non-statin therapy may be considered for CV benefit.
  - c. Depending on the additional desired LDL percentage reduction, either ezetimibe or a PCSK9 inhibitor can be considered in combination with statin therapy in very high-risk patients.
  - d. Both ezetimibe and PCSK9 inhibitors (given in combination with statins) reduce CV end points.
  - e. An LDL goal of less than 70 mg/dL is reasonable in patients post-ACS.
6. Pain control
  - a. NSAIDs and select cyclooxygenase-2 inhibitors (class III) should be discontinued at the time of presentation because they have been associated with an increased risk of major adverse cardiac events.
  - b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used to select therapy.
  - c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.
  - d. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy is insufficient.
    - i. Monitor regularly for sustained hypertension, edema, worsening renal function, or GI bleeding.
    - ii. If these occur, consider dose reduction or discontinuation.

7. Vaccination
    - a. Pneumococcal vaccination is recommended for patients 65 and older and in high-risk patients (including smokers with asthma) with CV disease.
    - b. An annual influenza vaccination is recommended for patients with CV disease.
  8. Patient education
    - a. All patients should be counseled on the duration of DAPT and the avoidance of premature discontinuation.
    - b. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.
    - c. Risk factor modification should be addressed in all patients after ACS.
  9. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.
- E. Special Populations
1. Antiplatelet recommendations in patients going on to CABG
    - a. Aspirin should be continued preoperatively to patients undergoing CABG (81–325 mg).
    - b. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days before surgery.
    - c. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding.
    - d. In patients referred for CABG, short-acting GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 hours before surgery to limit blood loss and transfusion.
  2. Combined oral anticoagulant therapy and antiplatelet therapy in patients with atrial fibrillation (AF) undergoing PCI
    - a. Triple therapy with an oral anticoagulant, low-dose aspirin, and a P2Y<sub>12</sub> inhibitor should be minimized because it substantially increases the risk of bleeding.
    - b. New AF guidelines and consensus recommendations based on clinical trial data represent a paradigm shift from older management with triple therapy:
      - i. Many trials have shown that double antithrombotic therapy (anticoagulant plus P2Y<sub>12</sub> inhibitor without aspirin) reduces bleeding events compared with triple therapy without signal for increasing ischemic events.
        - (a) Double therapy with a P2Y<sub>12</sub> inhibitor plus dose-adjusted vitamin K antagonist (WOEST trial)
        - (b) Double therapy with a P2Y<sub>12</sub> inhibitor plus rivaroxaban 15 mg daily (PIONEER AF)
        - (c) Double therapy with a P2Y<sub>12</sub> inhibitor plus dabigatran 150 mg twice daily (RE-DUAL)
        - (d) Double therapy with a P2Y<sub>12</sub> inhibitor plus apixaban 5 mg twice daily (AUGUSTUS)
      - ii. De-escalation time from triple to dual therapy varies depending on ischemic and bleeding risks.
        - (a) Aspirin therapy can be discontinued at time of discharge or can be continued for 1–3 months, depending on risks.
        - (b) Triple therapy may be extended beyond hospital discharge for a limited time (i.e., 1–3 months) in select patients at the highest risk of ischemic events and lowest risk of bleeding.
      - iii. In AF, direct-acting oral anticoagulants are preferred to vitamin K antagonists because of their reduced bleeding risk.
        - (a) Warfarin remains the drug of choice in patients with mechanical heart valves and in those with moderate to severe mitral stenosis.
        - (b) If warfarin is used for triple therapy, it is reasonable to maintain the international normalized ratio (INR) at the lower end of the therapeutic range (i.e., 2–2.5).

- iv. Clopidogrel is the preferred P2Y<sub>12</sub> inhibitor, though ticagrelor may be reasonable in patients at high ischemic/thrombotic and low bleeding risks (i.e., avoid prasugrel).
    - (a) Discontinue antiplatelet therapy at 1 year in most patients.
    - (b) However, the same considerations apply for shortening the duration (i.e., 6 months in those with high bleeding risk) and extending the duration (i.e., more than 12 months in those at high thrombotic risk with low bleeding risk) as for those without AF.
  - c. Proton pump inhibitors should be considered for those with a history of GI bleeding (and is reasonable in those without a known history of GI bleeding) who need triple antithrombotic therapy.
- 3. Older patients (i.e., 75 or older)
  - a. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
  - b. Bivalirudin, rather than GP IIb/IIIa inhibitors plus UFH, is reasonable in older patients, given its similar efficacy but less risk of bleeding (class IIa).
  - c. If enoxaparin is used as an anticoagulant in older patients (older than 75), the bolus should be omitted, and the dosing strategy should be 0.75 mg/kg subcutaneously every 12 hours; should not exceed 75 mg for the first two doses
  - d. CABG may be preferred to PCI in older patients, particularly those with diabetes mellitus or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.
- 4. Chronic kidney disease
  - a. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
  - b. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.
- 5. Women
  - a. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
  - b. Women derive the same benefit from aspirin, P2Y<sub>12</sub> inhibitors, anticoagulants,  $\beta$ -blockers, ACE inhibitors, and statins as men, but women may be at higher risk of adverse events.
    - i. Women have a higher rate of bleeding complications, renal failure, and vascular complications.
    - ii. A risk score has been developed to reduce bleeding risk.
  - c. Women with NSTEMI-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
  - d. Women with NSTEMI-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and the potential for harm (class III).
  - e. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be initiated for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks.
    - i. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
    - ii. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh the risk-benefit, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

**Patient Cases**

1. A 66-year-old woman (weight 70 kg) with a history of MI, hypertension, hyperlipidemia, and diabetes mellitus presents with sudden-onset diaphoresis, nausea, vomiting, and dyspnea, followed by a bandlike upper chest pain (8/10) radiating to her left arm. She had felt well until 1 month ago, when she noticed her typical angina was occurring with less exertion. Her ECG reveals ST-segment depression in leads II, III, and aVF and hyperdynamic T waves and positive cardiac enzymes. Blood pressure is 150/90 mm Hg, and all laboratory results are normal; SCr is 1.2 mg/dL. Home medications are aspirin 81 mg/day, simvastatin 40 mg every night, metoprolol 50 mg twice daily, and metformin 1 g twice daily. Which regimen is best for this patient?
  - A. Aspirin 325 mg, ticagrelor 180 mg one dose, and UFH 60-unit/kg bolus; then 12 units/kg/hour titrated to 50–70 seconds with an early invasive approach.
  - B. Aspirin 325 mg and enoxaparin 70 mg subcutaneously twice daily with an early invasive approach.
  - C. An ischemia-guided strategy with tirofiban 25 mcg/kg; then 0.15 mg/kg/minute plus enoxaparin 80 mg subcutaneously twice daily, aspirin 325 mg/day, and clopidogrel 300 mg one dose; then 75 mg once daily.
  - D. An ischemia-guided strategy with aspirin 325 mg and ticagrelor 180 mg one dose; plus UFH 70-unit/kg bolus; then 15 units/kg/hour.
2. A 45-year-old patient underwent an elective percutaneous transluminal coronary angioplasty and drug-eluting stent placement in her right coronary artery. Which best represents the minimum time DAPT should be continued?
  - A. 1 month.
  - B. 3 months.
  - C. 6 months.
  - D. 12 months.
3. A 52-year-old man (weight 100 kg) with a history of hypertension and hypertriglyceridemia presents at a major university teaching hospital with a cardiac catheterization laboratory. He has had 3 hours of crushing 10/10 substernal chest pain radiating to both arms that began while he was eating his lunch (seated), which is accompanied by nausea, diaphoresis, and shortness of breath. He has never before had chest pain of this character or intensity. He usually can walk several miles without difficulty and smokes 1.5 packs/day of cigarettes. Home medications are lisinopril 2.5 mg/day and aspirin 81 mg daily. Current vital signs include heart rate 68 beats/minute and blood pressure 178/94 mm Hg. His ECG reveals a 3-mm ST-segment elevation in leads V<sub>2</sub>–V<sub>4</sub>, I, and aVL. Serum chemistry values are within normal limits. The first set of cardiac markers shows positive troponins, 0.8 mcg/L (normal defined as less than 0.1 mcg/L). Which regimen is best for this patient's STEMI?
  - A. Reperfusion with primary PCI and stenting of occluded artery, together with tirofiban 25 mcg/kg; then 0.15 mg/kg/minute, clopidogrel 300 mg one dose, and aspirin 325 mg one dose.
  - B. Reperfusion with a reteplase 10-unit bolus twice, 30 minutes apart, plus a UFH 60-unit/kg bolus and a 12-unit/kg/hour infusion, clopidogrel, and aspirin.
  - C. Reperfusion with tenecteplase 25-mg intravenous push one dose, enoxaparin 30-mg intravenous bolus plus 100 mg subcutaneously twice daily, aspirin 325 mg one dose, ticagrelor 180 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.
  - D. Reperfusion with primary PCI with stenting, prasugrel 60 mg one dose, aspirin 325 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

**Patient Cases (Cont'd)**

4. A 76-year-old male smoker (weight 61 kg) has a history of hypertension, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to have substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. These episodes have increased in frequency to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the ED of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen (BUN) 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 ng/L (normal value less than 0.1 ng/L). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the ED. The nearest hospital with a catheterization laboratory facility is 2½ hours away. Which regimen is best?
- A. Give alteplase 15 units intravenously plus enoxaparin 30-mg intravenous bolus.
  - B. Use an ischemia-guided treatment strategy with UFH 4000-unit intravenous bolus, followed by 800 units intravenously per hour.
  - C. Give tenecteplase 35 mg intravenously plus UFH 4000-unit intravenous bolus followed by 800 units intravenously per hour.
  - D. Transfer the patient to a facility for primary PCI.

**II. ACUTE DECOMPENSATED HEART FAILURE**

- A. Precipitating Factors
  - 1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)
  - 2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, AF or other arrhythmias, concurrent infections, other acute CV disorders)
- B. Diagnosis
  - 1. Must include a detailed history and physical examination
  - 2. B-type natriuretic peptide (BNP) or NT-proBNP is useful to support the diagnosis and establish the prognosis for acute decompensated heart failure (ADHF).
    - a. Useful for excluding ADHF in patients with dyspnea of unknown etiology (ADHF can be excluded when results are less than 100 pg/mL and less than 300 pg/mL, for BNP and NT-proBNP, respectively)
    - b. NT-proBNP cutpoints of 450, 900, and 1800 pg/mL (for ages younger than 50, 50–75, and older than 75, respectively)
    - c. May be elevated with older age, female sex, renal dysfunction, and other cardiopulmonary disorders like pulmonary embolism
    - d. NT-proBNP is preferred in patients receiving angiotensin receptor neprilysin inhibitor (ARNI) therapy because BNP concentrations may be affected by ARNI therapy
  - 3. Hemodynamic monitoring (Table 13)
    - a. Routine use of hemodynamic monitoring with invasive intravenous lines (e.g., Swan-Ganz pulmonary artery catheters) is not recommended; however, signs and symptoms of congestion and perfusion (Table 14) or noninvasive means to determine hemodynamic values are commonly used to determine status of decompensation.

- b. Hemodynamic monitoring with pulmonary artery catheters helps in evaluating patients refractory to initial therapy, patients with unknown or unclear volume status, and patients with clinically significant hypotension or worsening renal function.
- c. Use of hemodynamic monitoring for mechanical circulatory support is beyond the scope of this chapter.

**Table 13.** Hemodynamic Values in Patients with ADHF and Sepsis

Parameter	Normal Value	Typical ADHF Value	Typical Sepsis Value
Mean arterial pressure <sup>a</sup> (MAP; mm Hg)	80–100	60–80	60–80
Heart rate (HR; beats/min)	60–80	70–90	90–100
Cardiac output (CO; L/min) <sup>b</sup>	4–7	2–4	5–8
Cardiac index (CI; L/min/m <sup>2</sup> ) <sup>c</sup>	2.8–3.6	1.3–2	3.5–4
Pulmonary capillary wedge pressure (mm Hg) <sup>d</sup>	8–12 <sup>b</sup>	18–30	5–8
Systemic vascular resistance (SVR; dynes/s/cm <sup>2</sup> ) <sup>e</sup>	900–1400	1500–3000	300–800
Central venous pressure (CVP; mm Hg)	2–6	6–15	2–6

BP = CO × SVR.

<sup>a</sup>MAP = diastolic blood pressure (DBP) + [⅓(SBP – DBP)].

<sup>b</sup>CO = stroke volume × HR.

<sup>c</sup>CI = CO/body surface area.

<sup>d</sup>15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.

<sup>e</sup>SVR = [(MAP – CVP)/CO] × 80.

ADHF = acute decompensated heart failure; SVR = systemic vascular resistance.

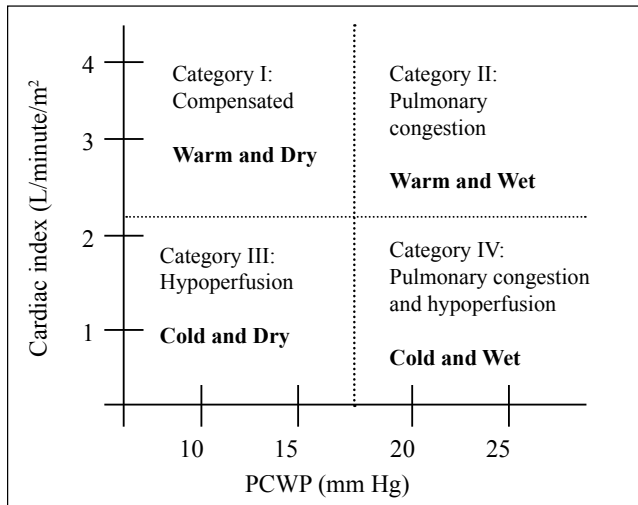
### C. Clinical Presentation

1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function (Figure 2).
2. “Wet or dry” is commonly used to describe volume status.
3. “Warm or cold” is used to describe cardiac function or ability to perfuse tissues.

**Table 14.** Signs and Symptoms of ADHF

Congestion (elevated PCWP)	Hypoperfusion (low CO)
Dyspnea on exertion or at rest	Fatigue
Orthopnea, paroxysmal nocturnal dyspnea	Altered mental status or sleepiness
Peripheral edema	Cold extremities
Rales	Worsening renal function
Early satiety, nausea, or vomiting	Narrow pulse pressure
Ascites	Hypotension
Hepatomegaly, splenomegaly	Hyponatremia
Jugular venous distension	
Hepatojugular reflux	

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.



**Figure 2.** Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in acute decompensated heart failure.

PCWP = pulmonary capillary wedge pressure.

#### D. ADHF Therapy Overview (Box 1; Table 15)

1. Address any precipitating factors, when possible.

#### Box 1. Overview of ADHF Guideline Recommendations

##### Diuretic therapy

Recommended as IV loop diuretics for patients with fluid overload. Change to PO route on day before discharge, if possible

When response to diuretics is minimal, the following options should be considered:

- Fluid and sodium restriction
- Initiation of increased doses or continuous infusion of loop diuretic
- Addition of a second diuretic with a different mechanism of action (metolazone, hydrochlorothiazide, chlorothiazide)
- Ultrafiltration

##### Inotropic therapy

May be considered to relieve symptoms and improve end-organ function in patients with reduced LVEF and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if

- Marginal SBP (< 90 mm Hg)
- Symptomatic hypotension despite adequate filling pressure
- No response to or intolerance of IV vasodilators

May be considered in similar patients with evidence of fluid overload if they respond poorly to IV diuretics or manifest diminished or worsening renal function

##### Vasodilator therapy

May be considered in addition to IV loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension (if symptomatic hypotension absent)

May be considered in patients with persistent symptoms despite aggressive diuretics and PO drug therapy

When adjunctive therapy is necessary in addition to loop diuretics, IV vasodilators should be considered over inotropic drugs

ADHF = acute decompensated heart failure; IV = intravenous(ly); LVEF = left ventricular ejection fraction.



2. Relieve signs and symptoms of congestion and tissue hypoperfusion.
  - a. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
  - b. No therapy studied to date has been shown conclusively to decrease mortality.
  - c. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events and are guided by cardiac output (CO) and volume status.
3. Reduce in-hospital mortality and minimize risk of rehospitalization.
4. Optimize GDMT.

**Table 15.** General ADHF Management Based on Hemodynamic Subset<sup>a</sup>

Subset and Description	Treatment
<b>Subset I: Warm and Dry</b> (normal parameters) (PCWP 15–18 mm Hg <sup>b</sup> and CI > 2.2 L/min/m <sup>2</sup> )	Optimize guideline-directed medical therapies (PO medications)
<b>Subset II: Warm and Wet</b> (pulmonary or peripheral congestion) (PCWP > 18 mm Hg and CI > 2.2 L/min/m <sup>2</sup> )	IV diuretics at a dose that equals or exceeds pre-admission dose (up to 2.5-fold) ± IV vasodilators (venous <sup>c</sup> ) for rapid relief of pulmonary congestion or (arterial) in the absence of hypotension If symptoms persist, adjunctive strategies <sup>d</sup> to overcome diuretic resistance may be necessary
<b>Subset III: Cold and Dry</b> (hypoperfusion ± orthostasis) (PCWP 15–18 mm Hg <sup>b</sup> and CI < 2.2 L/min/m <sup>2</sup> )	If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg If PCWP ≥ 15 mm Hg, SBP < 90 mm Hg, IV inotrope <sup>e</sup> If PCWP ≥ 15 mm Hg, SBP ≥ 90 mm Hg, IV vasodilator (arterial <sup>f</sup> ) ± IV vasopressor, <sup>g</sup> if needed
<b>Subset IV: Cold and Wet</b> (pulmonary/peripheral congestion + hypoperfusion) (PCWP > 18 mm Hg and CI < 2.2 L/min/m <sup>2</sup> )	IV diuretics + If SBP ≥ 90 mm Hg, IV vasodilator (arterial <sup>f</sup> ) If SBP < 90 mm Hg, IV inotrope <sup>e</sup> ± IV vasopressor, <sup>g</sup> if needed

<sup>a</sup>Patients may be categorized into a hemodynamic subset on the basis of signs and symptoms or invasive hemodynamic monitoring.

<sup>b</sup>Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.

<sup>c</sup>Venous vasodilator: Reduces PCWP.

<sup>d</sup>Adjunctive strategies for overcoming diuretic resistance include increasing the loop diuretic dose; changing to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and, in select patients, using ultrafiltration or a vasopressin antagonist.

<sup>e</sup>Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.

<sup>f</sup>Arterial vasodilator: Reduce systemic vascular resistance with compensatory increase in CI.

<sup>g</sup>IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF.

CI = cardiac index; IV = intravenous(ly); IVF = intravenous fluid; PCWP = pulmonary capillary wedge pressure; PO = oral(ly).

#### E. Chronic HF Therapy in the Setting of Acute Decompensation

1. It is recommended to continue guideline-directed medical therapies (GDMTs) during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock) because discontinuing GDMT worsens outcomes.
2. ACE inhibitors/ARBs, ARNIs
  - a. Caution with initiation or titration during aggressive diuresis
  - b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.
  - c. Consider discontinuation if worsening renal function after recent drug initiation or increased symptomatic hypotension, severe hyperkalemia (K greater than 5.5 mEq/L)

3.  $\beta$ -Blockers
    - a. Do not discontinue in patients whose condition is stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).
    - b. Consider discontinuation if ADHF caused by recent drug initiation or increase, evidence of new or worsening low output or cardiogenic shock, symptomatic hypotension or bradycardia
    - c. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.
    - d. Should be initiated at a low dose only in stable, euvolemic patients
    - e. Caution should be used when initiating in patients who have received inotropes during their hospital course.
  4. Digoxin
    - a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.
    - b. Consider discontinuation in symptomatic bradycardia, life-threatening arrhythmias, elevated concentrations, or signs/symptoms of digoxin toxicity.
    - c. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.
    - d. Caution if renal function begins to deteriorate or often fluctuates
- F. Diuretics (Box 2; Table 16): Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF
1. Considered first-line therapy for management of ADHF associated with fluid overload
  2. No difference between bolus and continuous administration of intravenous diuretics
  3. Administering high-dose intravenous diuretic (2.5 times the previous oral dose) is associated with greater fluid removal.

**Box 2. Diuretic Therapy for ADHF**

<b>Loop diuretics (ascending limb of loop of Henle)</b> Most widely used and most potent, effective at low CrCl (< 30 mL/min) Furosemide most commonly used; furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg PO
<b>Thiazides (distal tubule)</b> Weak diuretics when used alone, less effective at low glomerular filtration rate (CrCl < 30 mL/min) Reserved for add-on therapy when refractory to loop diuretics
<b>Diuretic resistance</b> Increase dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide) Add a second diuretic with a different mechanism of action <ul style="list-style-type: none"> <li>• Hydrochlorothiazide 25–50 mg PO daily,<sup>a</sup> metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration)</li> <li>• Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is very expensive; reserve for NPO or refractory to other alternatives</li> </ul> Continuous infusion of loop diuretic: Furosemide 0.1 mg/kg/hr IV doubled every 4–8 hr, max 0.4 mg/kg/hr
<b>Adverse effects:</b> Electrolyte depletion (sodium, K <sup>+</sup> , magnesium), worsening renal function

<sup>a</sup>Ceiling dose may vary depending on the CrCl.

GI = gastrointestinal; NPO = nothing by mouth.

**Table 16.** Loop Diuretic Pharmacokinetic and Pharmacodynamic Comparisons

Drug	Furosemide	Bumetanide	Torsemide	Ethacrynic Acid
PO equivalent dose	40 mg	1 mg	20 mg	50 mg
Bioavailability, %	10%–100% (avg 50%)	80%–100%	70%–100%	100%
PO to IV conversion	2:1	1:1	1:1	1:1
Usual maintenance dose	40–160 mg	1–5 mg	10–20 mg	25–50 mg
Ceiling dose (normal CrCl)	~160 mg	1–2 mg	10–20 mg	~200 mg
Onset (peak), PO	30–60 min (1 hr)	30–60 min (1–2 hr)	60 min	30 min
Onset of action (IV)	5 min	2–3 min	10 min	5 min
Metabolism	50% renal conjugation	50% hepatic	80% hepatic	66% renal
Half-life normal (HF)	1.5–2 hr (2.7 hr)	1 hr (1.3 hr)	3–4 hr (6 hr)	1–4 hr
Avg duration of effect	6–8 hr	4–6 hr	12–16 hr	6 hr

avg = average.

## G. Vasodilator Therapy (Table 17)

1. Used (with diuretics) primarily to manage pulmonary congestion or wet (subset II or IV) HF
  - a. Use is limited to relief of dyspnea in those with intact blood pressure.
  - b. No data to suggest intravenous vasodilators improve outcomes
2. When adequate blood pressure is maintained, use in preference to inotropic therapy.
3. Venodilators increase venous capacitance, resulting in lower preload to reduce myocardial stress.
  - a. Limits ischemia and helps preserve cardiac tissue (i.e., nitroglycerin would be the drug of choice for patients with ADHF and active ischemia)
  - b. Produces rapid symptomatic benefit by reducing pulmonary congestion (i.e., acute relief of shortness of breath while awaiting the onset of diuretic effects)
  - c. Nitroglycerin is commonly used as a venodilator.
4. Vasodilators with arterial vasodilating properties (nitroprusside) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low CO.
  - a. Sodium nitroprusside is usually reserved for patients:
    - i. With invasive hemodynamic monitoring (i.e., pulmonary artery catheter)
    - ii. Without end-organ dysfunction (i.e., to avoid cyanide and thiocyanate accumulation)
    - iii. Only until hemodynamic stabilization is achieved
    - iv. To ensure the reversibility of pulmonary hypertension during evaluation for mechanical circulatory support or transplantation
  - b. Nesiritide was discontinued by the manufacturer in February 2018.
5. Vasodilators should be avoided in patients with symptomatic hypotension (i.e., SBP less than 90 mm Hg).
6. Frequent blood pressure monitoring is necessary.

**Table 17.** Vasodilator Therapy for ADHF

	<b>Sodium Nitroprusside (Nipride)</b>	<b>IV Nitroglycerin</b>
Mechanism of action	Nitric oxide–induced stimulation of GC to convert GTP to cGMP	Combines with sulfhydryl groups in vascular endothelium to create <i>S</i> -nitrosothiol compounds that mimic nitric oxide’s stimulation of GC and production of cGMP
Clinical effects	Balanced arterial and venous vasodilator	Preferential venous vasodilator > arterial vasodilator, arterial vasodilation at high doses
Indication	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises	Warm and wet ADHF, ACS, or hypertensive crises
Dosing	0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/min every 10–20 min	5 mcg/min IV, increase by 5 mcg/min every 5–10 min up to 200 mcg/min
Typical dose	0.5–1 mcg/kg/min IV	25–100 mcg/min IV, titrated to response
Half-life	< 10 min	1–3 min
Elimination	Cyanide hepatically metabolized, thiocyanate renally excreted	Inactive metabolites in urine
AEs	Hypotension or cyanide or thiocyanate toxicity	Hypotension, reflex tachycardia, headache, tachyphylaxis

AE = adverse effect; cGMP = cyclic guanine monophosphate; GC = guanylate cyclase; GTP = guanosine triphosphate.

#### H. Inotropic Therapy (Table 18)

- Used primarily to manage hypoperfusion or cold (subset III or IV) HF
  - Useful for symptom relief in patients with a low SBP (less than 90 mm Hg) or symptomatic hypotension
  - Useful in patients with end-organ dysfunction (i.e., acute kidney injury, altered mental status, systemic hypoperfusion, hypotension, or CV collapse)
  - Useful in patients whose disease is refractory to other HF therapies
  - Useful as a bridge to an LV assist device or to a heart transplant or as palliative care
- It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure [PCWP] 15–18 mm Hg) before administering inotropic therapy.
- Given the risk of sequelae, it is reasonable to consider vasodilators before inotropes.
  - Both milrinone and dobutamine are proarrhythmic.
  - Inotropes increase mortality compared with vasodilator therapy.
- Monitor continuously for arrhythmias.
- Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages, but the choice of inotropic therapy is very individualized.
  - Milrinone may be favored:
    - To avoid tapering or discontinuing home  $\beta$ -blocker
    - When pulmonary artery pressures are high
  - Dobutamine may be favored in:
    - Severe hypotension
    - Bradycardia
    - Thrombocytopenia
    - Severe renal impairment

**Table 18.** Inotropic Therapy for ADHF

	<b>Dobutamine (Dobutrex)</b>	<b>Milrinone (Primacor)</b>
Mechanism of action	$\beta$ 1-Agonist: Stimulates AC to convert ATP to cAMP to $\uparrow$ CO; slight peripheral vasodilation	PDE inhibitor: Inhibits cAMP breakdown in heart to $\uparrow$ CO and in vascular smooth muscle to $\downarrow$ SVR
Clinical effects	Positive inotropic, chronotropic, lusitropic effects	Positive inotropic and lusitropic effects, no direct chronotropic effects
Indication	ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP > 15 mm Hg)	
Dosing	Start 2.5–5 mcg/kg/min IV; may titrate to max of 20 mcg/kg/min	50 mcg/kg IVB (rarely administered), then 0.1–0.2 mcg/kg/min IV; may titrate to max of 0.75 mcg/kg/min
Typical dose	5 mcg/kg/min IV	No bolus, 0.1–0.375 mcg/kg/min IV
Half-life	2 min	1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min
Elimination	Hepatically metabolized (inactive), renally eliminated	90% renal
AEs	Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use	Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use
Other comments	Consider in severe hypotension	Consider if receiving a $\beta$ -blocker or in those with high pulmonary artery pressures

AC = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CO = cardiac output; PDE = phosphodiesterase; SVR = systemic vascular resistance.

### I. Vasopressin Antagonists

- Use is limited because of their significant cost and their limited effects on meaningful long-term ADHF outcomes.
  - Should be viewed as “add on” therapy to aggressive diuresis and not as initial or adjunctive therapy for fluid removal
  - Strict free water restriction is guideline recommended (expert opinion).
- Tolvaptan is FDA approved for clinically significant hyponatremia associated with HF.
  - In those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L)
  - In those with less marked hyponatremia (i.e., less than 135 mEq/L) having neurologic symptoms and who have no correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone)
- Clinical use:
  - Oral dosing: 15 mg daily; then titrated to 30–60 mg as needed
  - Pharmacology: Binds to and inhibits the  $V_2$  receptor, located in the renal tubule where water reabsorption is regulated
    - Exerts its clinical effect within 2–4 hours and lasts about 24 hours
    - Increases serum sodium by about 2–4 mEq/L within 12–24 hours
    - Increases net urinary output and reduces total body weight (1–2 kg)
  - Initiate only in the hospital setting to allow monitoring of volume status and serum sodium concentrations.
  - An overly rapid rise in serum sodium (maximum correction in any 24-hour period of chronic hyponatremia should be less than 9 mEq/L) can result in hypotension, hypovolemia, and neurologic

- sequelae.
- e. Contraindicated with CYP3A4 inhibitors (tolvaptan is a substrate of 3A4) and in those with an eCrCl less than 10 mL/minute
- f. The FDA warns against use beyond 30 days (i.e., hepatotoxicity).
- g. Trials show effectiveness in correcting sodium with maintained therapy but no improvement in global clinical status or mortality and no reductions in rehospitalization.
  - i. Role in long-term management of HF remains unclear.
  - ii. Hyponatremia redevelops after therapy cessation.

**Patient Case**

*Questions 5–7 pertain to the following case.*

A 72-year-old man is admitted to the hospital for HF decompensation. The patient has progressively increased dyspnea when walking (now 10 ft [3 m], previously 30 ft [6 m]) and orthopnea (now four pillows, previously two pillows), increased bilateral lower-extremity swelling (3+), 13 kg of weight gain in the past 3 weeks, and dietary nonadherence. He has a history of idiopathic dilated cardiomyopathy (LVEF 25%, NYHA class III), paroxysmal AF, and hyperlipidemia. Pertinent laboratory values are as follows: BNP 2300 pg/mL (0–50 pg/mL),  $K^+$  4.9 mEq/L, BUN 32 mg/dL, SCr 2.0 mg/dL (baseline 1.9 mg/dL), aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase 42 IU/L, INR 1.3, aPTT 42 seconds, blood pressure 108/62 mm Hg, heart rate 82 beats/minute, and  $SAO_2$  95%. Home medications include carvedilol 12.5 mg twice daily, lisinopril 40 mg/day, furosemide 80 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day.

5. Which regimen is best for treating his ADHF?
  - A. Carvedilol 25 mg twice daily.
  - B. Sodium nitroprusside 0.1 mcg/kg/min IV.
  - C. Furosemide 120 mg intravenously twice daily.
  - D. Milrinone 0.5 mcg/kg/minute.
6. After being initiated on intravenous loop diuretics with only minimal urinary output, the patient is transferred to the coronary care unit for further management of diuretic-refractory decompensated HF. His  $SAO_2$  is now 87% on a 4-L nasal cannula, and an arterial blood gas is being obtained. His blood pressure is 110/75 mm Hg and heart rate is 75 beats/minute. The patient's SCr and  $K^+$  concentrations have begun to rise and are now 2.7 mg/dL and 5.4 mmol/L, respectively. In addition to a one-time dose of intravenous chlorothiazide, which regimen is most appropriate for this patient?
  - A. Nitroglycerin 20 mcg/minute.
  - B. Sodium nitroprusside 0.3 mg/kg/minute.
  - C. Dobutamine 5 mcg/kg/minute.
  - D. Milrinone 0.5 mcg/kg/minute.

**Patient Case (Cont'd)**

7. The patient initially responds with 2 L of urinary output overnight, and his weight decreases by 1 kg the next day. However, by day 5, his urinary output has diminished again, and his SCr has risen to 4.3 mg/dL. He was drowsy and confused this morning during rounds. His extremities are cool and cyanotic, blood pressure is 89/58 mm Hg, and heart rate is 98 beats/minute. It is believed that he is no longer responding to his current regimen. A Swan-Ganz catheter is placed to determine further management. Hemodynamic values are cardiac index 1.5 L/minute/m<sup>2</sup>, SVR 2650 dynes/second/cm<sup>5</sup>, and PCWP 30 mm Hg. Which regimen is most appropriate for his current symptoms?
- Milrinone 0.2 mcg/kg/minute.
  - Dobutamine 10 mcg/kg/minute.
  - Sodium nitroprusside 0.1 mcg/kg/minute.
  - Phenylephrine 20 mcg/minute.

**III. ACUTE LIFE-THREATENING ARRHYTHMIAS****A. Adult Cardiac Arrest (Box 3)****Box 3. Select ACLS Algorithms<sup>a</sup>**

1. Start CPR (give oxygen; attach monitor/defibrillator)
2. Rhythm shockable? (If yes, go to Pulseless VT/VF No. 3; if no, go to asystole/PEA No. 11)
<b>Algorithm for Pulseless VT or VF</b>
3. Defibrillation (shock 1)
4. CPR 2 min Establish IV/IO access <sup>a</sup>
5. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC, go to Asystole/PEA algorithm If ROSC, initiate post-cardiac arrest care
6. Defibrillation (shock 2)
7. CPR 2 min Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
<b>Algorithm for Pulseless VT or VF</b>
8. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC If ROSC, initiate post-cardiac arrest care
9. Defibrillation (shock 3)
10. CPR 2 min Amiodarone <sup>b</sup> 300 mg IV/IO × 1; may repeat at 150-mg bolus × 1; lidocaine may also be considered <sup>b</sup> Reversible causes of the event should be identified and corrected <sup>c</sup>

**Box 3. Select ACLS Algorithms<sup>a</sup> (Cont'd)**

<b>Algorithm for Asystole or PEA</b>
11. CPR 2 min Establish IV/IO access <sup>a</sup> Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
12. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, proceed
13. CPR 2 min Treat reversible causes <sup>c</sup>
14. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, continue steps 11–14 If ROSC, initiate post–cardiac arrest care

<sup>a</sup>If no IV/IO access, endotracheal administration of epinephrine, lidocaine, and atropine is allowed at 2–2.5 times the recommended IV/IO dose. Dilute this dose with 5–10 mL of sterile water or normal saline.

<sup>b</sup>If amiodarone is unavailable, lidocaine may be considered. Lidocaine 1–1.5 mg/kg IV, repeat 0.5–0.75 mg/kg IV/IO every 5–10 min (maximum 3 mg/kg). Lidocaine has not been shown to improve ROSC and hospital admission compared with amiodarone.

<sup>c</sup>Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia or hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).

ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

**B. Targeted Temperature Management (TTM) after cardiac arrest**

1. Indicated in adult patients who are comatose in whom return of spontaneous circulation (ROSC) has been achieved after cardiac arrest
  - a. Improves neurologic outcomes after ROSC
  - b. Optimal benefit for those in whom cooling begins soon after arrest
2. Cooling process
  - a. Goal temperature: 32°C–36°C
  - b. Duration: At least 24 hours after achieving the goal temperature
  - c. Slowly rewarmed at a typical rate of 0.3°C/hour until core body temperature is reached
3. Pharmacologic therapy during TTM
  - a. Shivering
    - i. Occurs when body temperature drops below 36°C and diminishes below 34°C
    - ii. Shivering increases heat production by 600% and increases oxygen consumption and is not desirable.
    - iii. Agents used to reduce shivering include meperidine, buspirone, clonidine, dexmedetomidine, and neuromuscular blocking agents.
  - b. Sedation
    - i. Required to minimize pain or anxiety
    - ii. Agents used to provide sedation include the combination of fentanyl, midazolam, or propofol.



- c. Other adverse effects related to hypothermia
  - i. Bradycardia – Lower heart rates are associated with improved outcomes; therefore, no aggressive correction is required.
  - ii. Electrolyte abnormalities
    - (a) Magnesium – Maintain serum magnesium concentrations at normal to high range.
    - (b) Potassium – Hypokalemia is common during the hypothermic phase, whereas hyperkalemia occurs during rewarming; avoid aggressive supplementation during hypothermia.
  - iii. Bleeding
    - (a) Increased risk because of impaired platelet function, reduced number of platelets, impaired production of clotting enzymes, etc.
    - (b) Monitor prothrombin time and aPTT once the temperature falls below 37°C.
  - iv. Arrhythmias
    - (a) If life-threatening arrhythmias occur during hypothermia, cooling should be discontinued.
    - (b) Treatment of life-threatening arrhythmias should generally follow advanced cardiac life support (ACLS) principles.
  - v. Hyperglycemia
    - (a) Hypothermia decreases insulin sensitivity and insulin secretion from the pancreas.
    - (b) Maintain blood glucose concentrations of 140–180 mg/dL during TTM.
  - vi. Hypotension
    - (a) Many patients require blood pressure support, and during TTM, a MAP above 80 mm Hg is preferred.
    - (b) Choice of vasoactive agents depends on patient heart rate, SBP, and risk of arrhythmias.
  - vii. Monitor for infection and hepatic impairment, and use adjunctive treatments as necessary.
- C. Symptomatic Bradycardia
  - 1. If unstable, atropine 1 mg every 3–5 minutes (maximum dose 3 mg). (Note: Unstable = hypotension, acutely altered mental status, signs of shock, ischemic chest discomfort, acute HF)
  - 2. If atropine fails, transcutaneous pacing, dopamine 5–20 mcg/kg/minute, or epinephrine 2–10 mcg/minute
- D. Symptomatic Tachycardia
  - 1. If unstable, synchronized cardioversion
  - 2. If stable, determine whether the QRS complex is narrow or wide.
    - a. Narrow-complex tachycardia (QRS less than 120 milliseconds); usually atrial arrhythmias
      - i. Regular ventricular rhythm: Supraventricular tachycardia (SVT) or sinus tachycardia likely
        - (a) Vagal maneuvers or adenosine 6-mg intravenous push, followed by a 20-mL saline flush, then a 12-mg intravenous push (may repeat once)
          - (1) Rapid push followed by elevation of arm to increase circulation
          - (2) Larger doses may be needed in patients taking theophylline or caffeine.
          - (3) Initial dose should be reduced to 3 mg in patients taking dipyridamole or carbamazepine and in patients after heart transplantation, and when the drug is being given by central access.
          - (4) Use adenosine cautiously in severe CAD.
          - (5) Adenosine should not be given to patients with asthma.
          - (6) Do not give adenosine for unstable or for irregular or polymorphic wide-complex tachycardias because it can cause degeneration to ventricular fibrillation (VF).

- (b) If vagal maneuvers or adenosine fails to convert paroxysmal SVT, calcium channel blockers (CCBs) or  $\beta$ -blockers can be used. If Wolff-Parkinson-White syndrome, avoid verapamil, diltiazem, and digoxin
- ii. Irregular (narrow complex) ventricular rhythm: AF (or possibly atrial flutter)
  - (a) General management should focus on control of the rapid ventricular rate.
    - (1) Usually non-dihydropyridine CCBs (diltiazem, verapamil) or  $\beta$ -blockers; digoxin sometimes useful
    - (2) Rate is acceptable if it is less than 110 beats/minute at rest in asymptomatic persistent AF.
  - (b) If the patient is hemodynamically unstable, synchronized cardioversion is recommended.
  - (c) Patients with AF for more than 48 hours are at high risk of cardioembolic events and should not be immediately cardioverted, if stable.
  - (d) Transesophageal echocardiography before cardioversion is an alternative strategy to ensure the absence of left atrial clot.
  - (e) Risk of thromboembolic event surrounding cardioversion (both pharmacologic and electrical) is greatest within the first 10 days.
  - (f) Cardioversion
    - (1) If AF for up to 7 days, either elective direct current conversion or chemical cardioversion
      - (A) Flecainide, dofetilide, propafenone, ibutilide, or amiodarone (proven efficacy)
      - (B) Digoxin and sotalol are not recommended and may be harmful.
      - (C) Disopyramide, quinidine, and procainamide are less effective or incompletely studied.
    - (2) If AF lasts greater than 7 days, administer either elective direct current conversion or chemical cardioversion with dofetilide, amiodarone, or ibutilide (proven efficacy).
- b. Wide-complex tachycardia (QRS greater than 120 milliseconds): Usually ventricular arrhythmias
  - i. VT or unknown mechanism
    - (a) Consider adenosine only if regular and monomorphic.
    - (b) Intravenous procainamide, amiodarone (or sotalol); lidocaine second line
    - (c) Avoid procainamide and sotalol if prolonged QTc.
  - ii. Definite SVT with aberrancy: Probably transiently slowed or converted by adenosine
  - iii. Polymorphic (irregular) VT
    - (a) Induced primarily when the QTc interval is greater than 500 milliseconds (torsades de pointes)
    - (b) If unstable, polymorphic (irregular) VT requires immediate defibrillation with the same strategy as VF.
    - (c) If stable, intravenous magnesium 1- to 2-g intravenous bolus (maximum 16 g every 24 hours) may be given; however, this is supported only by observational studies in the setting of wide QRS.
    - (d) Withdrawal of QT-prolonging medications, correction of low magnesium or  $K^+$  concentrations
      - (1) Class I and III antiarrhythmic drugs (AADs)
      - (2) Assess for drug interactions by CYP3A4 (e.g., azole antifungals, erythromycin).
      - (3) Assess for other QTc-prolonging drugs (e.g., haloperidol, ziprasidone, droperidol, promethazine, macrolide and quinolone antibiotics, tricyclic antidepressants, or drugs contraindicated with dofetilide such as sulfamethoxazole/trimethoprim or thiazides).

## E. AAD Overview (Tables 19 and 20)

**Table 19.** Vaughan-Williams AAD Classes

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
<b>Class I/Na<sup>+</sup> channel blockers</b>				
Ia (intermediate)	Disopyramide, quinidine, procainamide	↓ Conduction velocity; ↑ refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
Ib (fast)	Lidocaine, mexiletine, phenytoin	↓ Conduction velocity; ↑ refractory period	↓ QT interval	Ventricular arrhythmias
Ic (slow)	Flecainide, propafenone	↓↓↓ Conduction velocity; Ø refractory period	↑ QRS complex	Atrial and ventricular arrhythmias
Class II β-Blockers	Metoprolol, esmolol, atenolol	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
<b>Class III</b> K <sup>+</sup> channel blockers	Amiodarone, <sup>a</sup> dronedarone, <sup>a</sup> sotalol, <sup>b</sup> dofetilide, ibutilide	Ø Conduction velocity; ↑↑↑ refractory period	↑ QT interval	Atrial and ventricular arrhythmias
<b>Class IV</b> Ca <sup>2+</sup> channel blockers	Diltiazem, verapamil	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

<sup>a</sup>Amiodarone and dronedarone have Ib, II, and IV class activity in addition to class III actions.<sup>b</sup>Sotalol has 50%/50% β-blocking properties/K<sup>+</sup>-blocking properties.AAD = antiarrhythmic drug; Ca<sup>2+</sup> = calcium; HR = heart rate; Na<sup>+</sup> = sodium. ↑ = increases; ↓ = decreases; Ø = no effect.**Table 20.** AAD Properties and Dosing (class I and III agents only)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
<b>Class Ia: Na<sup>+</sup> channel blockers</b>		
Quinidine (Quinidex, Quinaglute)	AEs: Nausea, vomiting, and diarrhea (30%), “cinchonism” (CNS and GI symptoms, tinnitus), strong vagolytic and anticholinergic properties, TdP (first 72 hr), hypotension, GI upset PK: Half-life 5–9 hr Potent inhibitor of CYP2D6; substrate and inhibitor of CYP3A4 DIs: Warfarin, digoxin	AF conversion: Avoid use because of GI AEs AF and VT maintenance: Sulfate: 200–400 mg PO every 6 hr Gluconate (CR): 324 mg PO every 8–12 hr Decrease dose by 25% if CrCl < 10 mL/min
Procainamide (Pronestyl)	AEs: Hypotension (IV use, 5%), TdP CI: LVEF < 40% PK: Active metabolite NAPA (class III effects) may accumulate in renal dysfunction	AF conversion: 1 g IV for 30 min; then 2 mg/min (1-hr efficacy 51%) AF maintenance: No oral agent available VT conversion: 20 mg/min IV until 17 mg/kg, arrhythmia ceases, hypotension, or QRS widens > 50% VT maintenance: 1–4 mg/min Reduce dose in renal and liver dysfunction

**Table 20.** AAD Properties and Dosing (class I and III agents only) (*Cont'd*)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
<b>Class Ia: Na<sup>+</sup> channel blockers</b>		
Disopyramide (Norpace, Norpace CR)	AEs: Anticholinergic effects, TdP, ADHF (potent negative inotropic effect) CIs: Cardiogenic shock, congenital long QT syndrome, second- or third-degree AVB, glaucoma PK: Half-life 4–8 hr Substrate of CYP2D6 DI: May enhance the effect of $\beta$ -blockers	AF conversion: IR 200 mg (if < 50 kg) or 300 mg (if > 50 kg) PO every 6 hr AF maintenance: 400–800 mg/day in divided doses (recommended adult dose 600 mg/day given as IR 150 mg PO every 6 hr or as CR 300 mg PO every 12 hr) If < 50 kg, moderate renal dysfunction (CrCl > 40 mL/min) or hepatic dysfunction, max 400 mg/day If severe renal dysfunction (IR only; avoid CR) CrCl 30–40 mL/min, 100 mg every 8 hr CrCl 15–30 mL/min, 100 mg every 12 hr CrCl < 15 mL/min, 100 mg every 24 hr VTs: Use has fallen out of favor because of the availability of newer agents with less toxicity
<b>Class Ib: Na<sup>+</sup> channel blockers</b>		
Lidocaine (Xylocaine)	AEs: CNS (perioral numbness, seizures, confusion, blurry vision, tinnitus) CI: Third-degree AVB PK: Reduce dose in those with HF, liver disease, low body weight, and renal dysfunction and in older adults DI: Amiodarone (increased lidocaine concentrations)	Pulseless VT/VF conversion or VT with a pulse: 1–1.5 mg/kg IVP; repeat 0.5–0.75 mg/kg every 3–5 min (max 3 mg/kg) (If LVEF < 40%, 0.5–0.75 mg/kg IVP) (Amiodarone DOC in pulseless VT/VF; lidocaine acceptable if amiodarone not available) VT maintenance: 1–4 mg/min Reduce maintenance infusion in liver disease
Mexiletine (Mexitil)	AEs: CNS (tremor, dizziness, ataxia, nystagmus) CI: Third-degree AVB PK: Half-life 12–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP1A2	VT maintenance: 200–300 mg PO every 8 hr; max 1200 mg/day Reduce dose by 25%–30% in hepatic impairment
<b>Class Ic: Na<sup>+</sup> channel blockers (Note: Avoid in patients with HF or after MI; increased risk of sudden death)</b>		
Propafenone <sup>a</sup> (Rythmol, Rythmol SR)	AEs: Metallic taste, dizziness, ADHF, bronchospasm, bradycardia, heart block (negative inotropy and $\beta$ -blocking properties) CIs: HF (NYHA III–IV), liver disease, valvular disease (TdP), CAD, MI PK: Half-life 10–25 hr Substrate CYP2D6, CYP1A2, CYP3A4 Inhibitor CYP1A2, CYP2D6 DIs: Digoxin $\uparrow$ by 70%; warfarin $\uparrow$ by 50% as well as drugs that inhibit CYP 2D6, 1A2, 3A4 (increased propafenone)	AF conversion: 600 mg PO $\times$ 1 (efficacy 45% at 3 hr) 450 mg PO $\times$ 1 (weight < 70 kg) AF maintenance: HCl: 150–300 mg PO every 8–12 hr HCl (SR): 225–425 mg PO every 12 hr Reduce dose 70%–80% in hepatic impairment
Flecainide <sup>a</sup> (Tambocor)	AEs: Dizziness, tremor, ADHF (negative inotropy), vagolytic, anticholinergic, hypotension CIs: HF, CAD, valvular disease, LVH (TdP) PK: Half-life 10–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP2D6 DI: Digoxin $\uparrow$ by 25%	AF conversion: 300 mg PO $\times$ 1 (efficacy 50% at 3 hr) AF maintenance: 50–150 mg PO BID Reduce dose by 50% when CrCl < 35 mL/min

**Table 20.** AAD Properties and Dosing (class I and III agents only) (*Cont'd*)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
<b>Class III: K<sup>+</sup> channel blockers</b>		
Amiodarone (Cordarone)	<p>AEs: Pulmonary fibrosis 3%–17%, hyperthyroidism 3%, hypothyroidism 30%, neurologic toxicity 20%–40%, GI upset, photosensitivity, corneal deposits, hepatitis, blue-gray skin 15%, TdP &lt; 1%, heart block 14%, hypotension (IV), phlebitis (IV; Ca<sup>2+</sup>- and <math>\beta</math>-blocking properties), bradycardia</p> <p>CIs: Iodine hypersensitivity, hyperthyroidism, third-degree AV heart block</p> <p>PK: Half-life 58 days (avg)</p> <p>Inhibits CYP3A4/2D6/2C9/1A2/2C19 and intestinal P-gp</p> <p>Substrate CYP3A4/1A2/2C19/2D6</p> <p>DIs: Warfarin, digoxin, statins (max simvastatin dose 20 mg/day), phenytoin <math>\uparrow \geq 50\%</math>, lidocaine, and others</p> <p>Does not increase mortality in patients with HF</p>	<p>AF conversion:</p> <p>IV: 5–7 mg/kg IV over 30–60 min, then 1.2–1.8 g/day continuous IV or divided oral doses until 10 g</p> <p>PO: 1.2–1.8 g/day in divided doses until 10 g AF maintenance: 200–400 mg/day PO</p> <p>Pulseless VT/VF conversion:</p> <p>300 mg or 5 mg/kg IVB in 20 mL of D<sub>5</sub>W or NS; repeat 150 mg IVB every 3–5 min</p> <p>Stable VT: 150 mg IVB in 100 mL of D<sub>5</sub>W for 10 min</p> <p>VT/VF maintenance: 1 mg/min <math>\times</math> 6 hr, then 0.5 mg/min (max 2.2 g/day)</p>
Sotalol (Betapace, Betapace AF)	<p>AEs: ADHF, bradycardia, AVB, wheezing, 3%–8%</p> <p>TdP within 3 days of initiation, bronchospasm (<math>\beta</math>-blocking effects)</p> <p>CIs: Baseline QTc &gt; 440 ms or CrCl &lt; 40 mL/min (AF only), LVEF &lt; 40%</p> <p>PK: Renally eliminated, half-life 30–40 hr</p> <p>Hospitalization ideal for initiation of therapy because of BW: Do not initiate if baseline QTc interval &gt; 450 ms; if QTc &gt; 500 ms during therapy, reduce the dose, prolong the infusion duration, or d/c use</p> <p>Not effective for AF conversion</p>	<p>AF maintenance (based on CrCl):</p> <p>80 mg PO BID (&gt; 60 mL/min) 80 mg PO daily (40–60 mL/min) CI &lt; 40 mL/min</p> <p>VT maintenance (based on CrCl):</p> <p>80 mg PO BID (&gt; 60 mL/min) 80 mg PO daily (30–60 mL/min)</p> <p>80 mg PO every 36–48 hr (10–30 mL/min)</p> <p>80 mg PO: Individualize; every 48 hr minimum (&lt; 10 mL/min)</p> <p>IV dosing depends on target oral dose and creatinine clearance.</p>
Dofetilide (Tikosyn)	<p>AEs: TdP (0.8%; 4% if no renal adjustment), diarrhea</p> <p>CIs: Baseline QTc &gt; 440 ms or CrCl &lt; 20 mL/min or, CI in patients with intraventricular conduction delays with baseline QT &gt; 500 msec; NTE 550 msec</p> <p>PK: Renal and hepatic elimination</p> <p>Half-life 6–10 hr</p> <p>Substrate CYP3A4</p> <p>DIs: CYP3A4 inhibitors and drugs secreted by kidney (cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine, dolutegravir, megestrol), HCTZ</p> <p>BW: Hospitalization mandatory for initiation, obtain QTc 2–3 hr after each of the first five doses, reduce 50% if QTc <math>\uparrow</math> &gt; 15%; NTE QTc &gt; 500 ms</p> <p>Does not increase mortality in patients with HF</p>	<p>AF conversion (based on CrCl; efficacy 12% at 1 mo):</p> <p>500 mcg PO BID (&gt; 60 mL/min)</p> <p>250 mcg PO BID (40–60 mL/min)</p> <p>125 mcg PO BID (20–40 mL/min)</p> <p>CI &lt; 20 mL/min</p> <p>AF maintenance: Dose as above according to renal function; adjust for QTc NTE 500 ms or &gt; 15% <math>\uparrow</math> in QTc</p>

**Table 20.** AAD Properties and Dosing (class I and III agents only) (*Cont'd*)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
<b>Class III: K<sup>+</sup> channel blockers</b>		
Ibutilide (Corvert)	AEs: TdP 8%, AV heart block ( $\beta$ -blocking properties) CIs: Baseline QTc > 440 ms, LVEF < 30%, concomitant AADs PK: Half-life 2–12 hr (avg 6) DIs: CYP3A4 inhibitors or QT-prolonging drugs ECG monitoring during and 4 hr after DCC	AF conversion: 1 mg IV ( $\geq 60$ kg) or 0.01 mg/kg IV (< 60 kg); repeat in 10 min if ineffective (efficacy 47% at 90 min) BW: Potentially fatal arrhythmias (e.g., polymorphic VT) can occur with ibutilide, usually in association with TdP; patients with chronic AF may not be the best candidates for ibutilide conversion
Dronedarone (Multaq)	AEs: Worsening HF, QT prolongation, hypokalemia or hypomagnesemia with K <sup>+</sup> -sparing diuretics, hepatic failure CIs: QTc $\geq 500$ ms or PR $\geq 280$ ms, NYHA class IV HF or NYHA class II–III HF with recent ADHF, severe hepatic impairment, second- or third-degree AVB, or HR < 50 beats/min PK: Half-life 13–19 hr Substrate 3A4 Inhibitor intestinal P-gp DIs: CYP3A4 inhibitors, QT-prolonging drugs, simvastatin, tacrolimus/sirolimus, warfarin, and other CYP3A4 substrates with narrow therapeutic range, digoxin and other P-gp substrates (dabigatran, rivaroxaban)	AF maintenance: 400 mg orally BID d/c if QTc $\geq 500$ ms BW: Risk of death is doubled when used in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; use is contraindicated in these patients Use in patients with permanent AF doubles the risk of death, stroke, and hospitalization for HF; use is contraindicated in patients with AF who will not or cannot be converted to normal sinus rhythm

<sup>a</sup>Indicates that pill-in-pocket approach can be used for selected patients.

AV = atrioventricular; AVB = atrioventricular block; CAD = coronary artery disease; CI = contraindication; CNS = central nervous system; CR = controlled release; d/c = discontinue; DCC = direct current cardioversion; D<sub>5</sub>W = dextrose 5%; DI = drug interaction; DOC = drug of choice; HCl = hydrochloride; HCTZ = hydrochlorothiazide; HR = heart rate; IR = immediate release; LVH = left ventricular hypertrophy; ms = millisecond(s); NAPA = *N*-acetylprocainamide; NS = normal saline; NTE = not to exceed; NYHA = New York Heart Association; PK = pharmacokinetics; QTc = corrected QT interval; SR = sustained release; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

## F. Long-term Management of Ventricular Arrhythmias

### 1. Nonsustained VT

#### a. Asymptomatic

- Infrequent ventricular ectopic beats, couplets, and triplets without other signs of underlying structural heart disease (SHD) or inherited arrhythmia syndrome should be considered a normal variant in asymptomatic patients.
- No treatment other than reassurance is needed for patients without SHD or inherited arrhythmia disorder.
- Treat survivors of MI and HFrEF with  $\beta$ -blockers (class I), unless contraindicated.

#### b. Symptomatic

- $\beta$ -Blockers may be considered for a therapeutic trial in symptomatic patients (class IIb, level of evidence [LOE] C).
- Non-dihydropyridine CCBs may be considered as an alternative to  $\beta$ -blocker therapy in suitable patients without SHD.

- iii. AAD therapy (amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmias in patients receiving adequate doses of a  $\beta$ -blocker or CCB (class IIb; LOE C).
    - (a) Flecainide and propafenone are not recommended to suppress premature ventricular contractions in patients with reduced LV function (class III).
    - (b) Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with a prolonged QT interval at baseline or excessive prolongation of QT interval (500 milliseconds) on therapy initiation (class I; LOE B).
    - (c) Amiodarone appears to have less overall proarrhythmic risk than other AADs in patients with HF and may be preferred to other membrane-active AADs unless a functioning defibrillator has been implanted (class IIb; LOE C).
  - iv. Amiodarone, sotalol, and other  $\beta$ -blockers are useful after defibrillator implantation to reduce shocks and suppress nonsustained VT in patients who are unsuitable for ICD therapy, in addition to optimal medical therapy for patients with HF.
- 2. Sustained VT
    - a. Immediate defibrillation (ACLS management)
    - b. Evaluate cardiac structure and function.
    - c. ICDs indicated for most patients with SHD
- G. Implantable Cardioverter-Defibrillators
- 1. For primary prevention of SCD
    - a. Previous MI, at least 40 days earlier, and EF of 35% or less
    - b. Nonischemic dilated cardiomyopathy, LVEF of 35% or less receiving optimal chronic medications for at least 3 months
    - c. Syncope with SHD and inducible VT/VF during electrophysiologic study
    - d. High risk of life-threatening VT/VF; congenital long QT syndrome with recurrent symptoms or torsades de pointes while receiving a  $\beta$ -blocker
    - e. Must have reasonable survival expectation for more than 1 year
  - 2. For secondary prevention of SCD
    - a. Previous episode of resuscitated VT/VF, hemodynamically unstable VT with no completely reversible cause, or sustained VT in presence of heart disease
    - b. Must be receiving optimal chronic medications ( $\beta$ -blockers, ACE inhibitors)
    - c. Must have reasonable survival expectation for more than 1 year
  - 3. General medication considerations with ICD (Table 21)
    - a.  $\beta$ -Blockers
      - i. Considered mainstay therapy
      - ii. Effective in suppressing ventricular ectopic beats and in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (nonsustained VT)
    - b. Amiodarone
      - i. No better than ICD in reducing SCD as a lone agent; no mortality benefit
      - ii. Can be used to treat symptomatic nonsustained VT if  $\beta$ -blockers not effective when ICD not indicated
      - iii. Can be used in combination with  $\beta$ -blockers to decrease firing of ICD (defibrillator storm)
    - c. Sotalol
      - i. No mortality advantage
      - ii. Can suppress VT and be used to decrease frequency of ICD firing
      - iii. Greater proarrhythmic potential; avoid in patients with severely depressed LVEF or significant HF; renal dosing necessary

**Table 21.** Alteration of Defibrillation Threshold

Threshold Alteration	Medications	Comments
Increase threshold	Amiodarone, lidocaine, and mexiletine	Reprogram ICD, increased energy (joules) needed
Decrease threshold	Sotalol	May decrease energy needed for DCC

ICD = implantable cardioverter-defibrillator.

#### H. Treatment of Arrhythmias in Special Patient Populations

##### 1. Heart failure

- Avoid class Ia and class Ic agents.
- Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.
- Dronedarone (used in atrial arrhythmias only) is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; risk of death was doubled in these patients.

##### 2. Acute MI

- Avoid class Ia and class Ic agents.
- CAST trial with class Ic agents (encainide, flecainide) showed greater mortality when used to treat post-MI non-life-threatening ventricular arrhythmias; avoid class Ic agents in patients with SHD.
- Class Ia medications: Increased mortality in MI survivors
- Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.

#### I. Drug-Induced Arrhythmias: Review all potential drug etiologies and treat appropriately.

##### 1. Drug-induced QT prolongation

- Discontinue offending agent if QT prolongation is significant (i.e., greater than 450 milliseconds).
- Ensure proper renal and hepatic dosing adjustments.
- Review electrolyte abnormalities and thyroid function tests.
- Ensure that all electrolytes are maintained at critical concentrations: K<sup>+</sup> greater than 4 mmol/L and less than 5 mmol/L and magnesium greater than 2 mg/dL.
- Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).

##### 2. Drug-induced bradycardia or atrioventricular block

- β-Blocker, CCB, digoxin
- Administer antidote, if appropriate (e.g., calcium for CCB toxicity).

##### 3. Review for drug interactions. AADs have drug interactions that may cause significant outcomes.



**Patient Cases**

*Questions 8 and 9 pertain to the following case.*

A 68-year-old man is admitted after an episode of syncope, with a presyncopal syndrome of seeing black spots and dizziness before passing out. Telemetry monitor showed sustained VT for 45 seconds. His medical history includes HF NYHA class III, LVEF 30%, two MIs, hypertension for 20 years, LV hypertrophy, DM, and diabetic nephropathy. His medications include lisinopril 5 mg/day, furosemide 20 mg twice daily, metoprolol 25 mg twice daily, digoxin 0.125 mg/day, glyburide 5 mg/day, atorvastatin 40 mg, and aspirin 81 mg/day. His blood pressure is 120/75 mm Hg, with heart rate 80 beats/minute, BUN 30 mg/dL, and SCr 2.2 mg/dL.

8. Which is the best therapy to initiate for conversion of his sustained VT?
  - A. Amiodarone 150 mg intravenously for 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute.
  - B. Sotalol 80 mg twice daily titrated to QTc of about 450 milliseconds.
  - C. Dofetilide 500 mcg twice daily titrated to QTc of about 450 milliseconds.
  - D. Procainamide 20 mg/minute, with a maximum of 17 mg/kg.
9. The patient presents to the ED 3 months after amiodarone maintenance initiation (he refused ICD placement) after a syncopal episode, during which he lost consciousness for 30 seconds, according to witnesses. He also has rapid heart rate episodes during which he feels dizzy and lightheaded. He feels very warm all the time (he wears shorts, even though it is winter), cannot sleep, and has lost 3 kg in weight. He received a diagnosis of hyperthyroidism caused by amiodarone therapy. On telemetry, he has runs of nonsustained VT. Which best predicts the duration of amiodarone-associated hyperthyroidism in this patient?
  - A. Never.
  - B. 1 month.
  - C. 6 months.
  - D. 18 months.
10. A 64-year-old woman presents to the ED with the chief concern of palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior-wall MI 6 months ago. She is pale and diaphoretic but can respond to commands. The patient's laboratory values are within normal limits. Her vital signs include blood pressure 95/70 mm Hg and heart rate 145 beats/minute; telemetry shows sustained VT. Although initially unresponsive to  $\beta$ -blockers, the patient is successfully treated with lidocaine. Subsequent electrophysiologic testing reveals inducible VT, and sotalol 80 mg orally twice daily is prescribed. Two hours after the second dose, the patient's QTc is 520 milliseconds. Which regimen change would be most appropriate for this patient?
  - A. Continue sotalol at 80 mg orally twice daily.
  - B. Increase sotalol to 120 mg orally twice daily.
  - C. Discontinue sotalol and initiate dofetilide 125 mcg orally twice daily.
  - D. Discontinue sotalol and initiate amiodarone 400 mg orally three times daily.

## IV. HYPERTENSIVE CRISES

### A. Definitions

1. Hypertensive emergency
  - a. Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage
  - b. Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, or other acute neurologic deficit; UA or acute MI; acute LV failure with pulmonary edema; dissecting aortic aneurysm; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia
  - c. Actual blood pressure may not be as important as the rate of blood pressure rise.
  - d. Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage
  - e. In general, oral therapy is discouraged for hypertensive emergencies.
2. Hypertensive urgency
  - a. Situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target-organ damage or dysfunction
  - b. Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.

### B. Goals and Treatment

1. Hypertensive emergency
  - a. Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.
  - b. Patients are usually admitted for intensive care unit care and close follow-up.
  - c. Lower MAP by no more than 25% in the first hour; then reduce SBP to 160 mm Hg and DBP to 100–110 mm Hg over next 2–6 hours; then to normal over next 24–48 hours
  - d. Exceptions:
    - i. Do not lower blood pressure in acute ischemic stroke unless greater than 220/120 mm Hg or greater than 185/110 mm Hg in tissue plasminogen activator candidates.
    - ii. Rapidly lower blood pressure to less than 140 mm Hg in the first hour of treatment in severe preeclampsia or eclampsia and in pheochromocytoma with hypertensive crisis.
    - iii. Rapidly lower blood pressure to less than 120 mm Hg in the first hour of treatment in aortic dissection.
  - e. Intravenous medications used commonly (Table 22)
  - f. No randomized evidence to suggest one drug of choice because of small trial size, lack of long-term follow-up, and failure to report outcomes
  - g. Two trials have shown that nicardipine is better than labetalol in achieving the short-term blood pressure target.
  - h. Agents are chosen on the basis of drug pharmacology, pathophysiologic factors underlying the patient's hypertension, degree of progression of target-organ damage, desirable rate of blood pressure decline, and presence of patient characteristics (Tables 22 and 23).
  - i. No randomized evidence exists comparing different strategies to reduce blood pressure, except in patients with intracranial hemorrhage.
  - j. No randomized evidence suggests how rapidly to reduce blood pressure.
  - k. Clinical experience indicates that excessive reductions in blood pressure can cause renal, cerebral, or coronary ischemia and should be avoided.

## 2. Hypertensive urgency

- Treated by reinstitution or intensification of antihypertensive drug therapy
- No indication for referral to the ED, immediate reduction in blood pressure in the ED, or hospitalization
- No proven benefit exists from rapid reductions in blood pressure.
- Choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate.
- All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).

## C. Treatment Options (Table 22)

**Table 22.** Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
<b>Vasodilators</b>		
Sodium nitroprusside (Nipride) (immediate, 2–3 min)	0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; max 10 mcg/kg/min; for infusion rates $\geq$ 4–10 mcg/kg/min or duration > 30 min, thiosulfate can be coadministered to prevent cyanide toxicity	Intra-arterial BP monitoring recommended to prevent “overshoot”; lower doses required in older adult patients; tachyphylaxis common with extended use AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurologic changes and cardiac arrest, nausea, vomiting, methemoglobinemia CIs: Renal, hepatic failure Caution: Elevated ICP
Nitroglycerin (2–5 min, 5–10 min)	5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a max 20 mcg/min	Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients AEs: Headache, nausea, vomiting, tachyphylaxis
Hydralazine (Apresoline) (10 min, 1–4 hr)	5–10 mg by slow IV infusion every 4–6 hr (NTE initial 20 mg/dose)	BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent AEs: Reflex tachycardia, headache, flushing Caution: Angina or MI, elevated ICP, aortic dissection
Enalaprilat (Vasotec) (within 30 min, 12–24 hr)	0.625–1.25 mg over 5 min; doses can be increased up to max 5 mg every 6 hr	Should not be used in acute MI; mainly useful in hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min) and unpredictability of BP response AEs: Renal insufficiency or failure, hyperkalemia CIs: Pregnancy, bilateral renal artery stenosis, angioedema (Note: Long half-life)

**Table 22.** Commonly Used IV Drugs for Hypertensive Emergencies (*Cont'd*)

Drug (onset, duration)	IV Dose	Comments/AEs
<b>Vasodilators</b>		
Fenoldopam (Corlopam) ( $< 5$ min, 30 min)	0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a max of 1.6 mcg/kg/min	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or ICP and those with sulfite allergy AEs: Headache, flushing, tachycardia, cerebral ischemia
Nicardipine (Cardene) (1–5 min, 15–30 min; up to 4 hr if prolonged infusion)	5 mg/hr, increased by 2.5 mg/hr every 5 min to a max 15 mg/hr	Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients AEs: Reflex tachycardia, nausea, vomiting, headache, flushing Caution: Angina or MI, acute HF
Clevidipine (Cleviprex) (2–4 min, 5–15 min)	1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; max 32 mg/hr; max duration 72 hr	Patients with renal failure and hepatic failure and older adults not specifically studied – use low-end range for older adults; contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g., pathologic hyperlipidemia, lipid nephrosis, or acute pancreatitis) Caution: HF, concomitant $\beta$ -blocker use, reflex tachycardia, rebound HTN
<b>Adrenergic Inhibitors</b>		
Esmolol (Brevibloc) (1–2 min, 10–30 min)	LD 500–1000 mcg/kg IVB over 1 min, then a 50-mcg/kg/min infusion; for additional BP lowering, the bolus dose is repeated, and the infusion is increased in 50-mcg/kg/min increments as needed to a max 200 mcg/kg/min	Contraindicated in patients with concurrent $\beta$ -blocker therapy, bradycardia, or decompensated HF AEs: Bronchospasm, HF exacerbation, bradycardia or heart block Caution: May worsen acute HF, asthma (higher doses may block $\beta_2$ -receptors and affect lung function in reactive airway disease), heart block
Labetalol (Normodyne, Trandate) (5–10 min, 3–6 hr)	20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to max 3 mg/kg/hr	Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia
Phentolamine (2 min, 15–30 min)	IVB dose 5 mg; additional bolus doses every 10 min as needed	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)

CI = contraindication; ICP = intracranial pressure.

**Table 23.** Agents Preferred for Hypertensive Crises According to Comorbidities

Comorbidity	Preferred Agents	Comments
Acute aortic dissection	Labetalol, esmolol	Requires rapid lowering of SBP to $\leq 120$ mm Hg within 20 min; $\beta$ -blocker should be given before vasodilator (nicardipine or NTP) if needed for BP control or to prevent reflex tachycardia or inotropic effect; SBP $\leq 120$ mm Hg should be achieved within 20 min
Acute coronary syndromes	Esmolol or NTG (preferred), labetalol, nicardipine	Nitrates given in the presence of PDE-5 inhibitors may induce profound hypotension; contraindications to $\beta$ -blockers include moderate to severe LV failure with pulmonary edema, right ventricular infarction, bradycardia ( $< 60$ beats/min), hypotension (SBP $< 100$ mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airway disease
Acute pulmonary edema	Clevidipine, NTG, NTP	$\beta$ -Blockers contraindicated; NTG preferred for ADHF
Acute renal failure	Clevidipine, fenoldopam, nicardipine	
Eclampsia or preeclampsia	Labetalol, nicardipine, hydralazine (second line)	Requires rapid BP lowering to $< 140$ mm Hg within first hour; ACE inhibitor, ARBs, renin inhibitors, and NTP contraindicated
Perioperative HTN (BP $\geq 160/90$ mm Hg or SBP elevation $> 20\%$ of the preoperative value that persists $> 15$ min)	Clevidipine, esmolol, nicardipine, NTG	Intraoperative HTN is most common during anesthesia induction and airway manipulation
Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status)	Clevidipine, nicardipine, phentolamine (Note: Avoid unopposed $\beta$ -blockade)	Requires rapid lowering of BP
Acute intracranial hemorrhage	IV continuous infusion	Lower BP in those who present with SBP $> 220$ mm Hg with continuous IV infusion and close BP monitoring; immediate lowering of SBP $< 140$ mm Hg is not of benefit and may be harmful. Avoiding medications that can increase ICP and worsen cerebral ischemia (hydralazine, NTG, and NTP)
Acute ischemic stroke	No preference of agent	Early initiation or resumption of antihypertensive treatment indicated only in (1) patients treated with tissue-type plasminogen activator to an SBP $< 185/110$ mm Hg and (2) patients with SBP $> 220$ mm Hg or DBP $> 120$ mm Hg; cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and rapid reduction of BP can be harmful; reinstitute antihypertensive therapies in those with preexisting HTN after neurologic stability

ARB = angiotensin receptor blocker; NTP = nitroprusside.

**Patient Cases**

11. A 68-year-old man with a history of stage 5 chronic kidney disease receiving hemodialysis, hypertension, CAD post-MI, moderately depressed LVEF, and gastroesophageal reflux disease presents with acute-onset shortness of breath and chest pain. After his recent dialysis, he was nonadherent to medical therapy for 2 days and noticed he had gained 2 kg in 24 hours. His baseline orthopnea worsened to sleeping sitting up in a chair for the 2 nights before admission. He admits smoking cocaine within the past 24 hours and developed acute-onset chest tightness with diaphoresis and nausea, and his pain was 7/10. He went to the ED, where his blood pressure was 250/120 mm Hg. He had crackles halfway up his lungs on examination, and chest radiography detected bilateral fluffy infiltrates with prominent vessel cephalization. His ECG revealed sinus tachycardia, heart rate 122 beats/minute, and ST-segment depressions in leads 2, 3, and aVF. He was admitted for a hypertensive emergency. Laboratory results are as follows: BUN 48 mg/dL, SCr 11.4 mg/dL, BNP 2350 pg/mL, troponin T 1.5 ng/L (less than 0.1 mcg/L), creatine kinase 227 units/L, and creatine kinase-MB 22 units/L. Which medication is best for this patient's hypertensive emergency?
- A. Intravenous nitroglycerin 5 mcg/minute titrated to a 25% reduction in MAP.
  - B. Labetalol 2 mcg/minute titrated to a 50% reduction in MAP.
  - C. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
  - D. Clonidine 0.1 mg orally every 2 hours as needed for a 50% reduction in MAP.
12. A 56-year-old white woman with a long history of hypertension because of nonadherence and recently diagnosed HF (EF 35%) presents to the local ED with blood pressure 210/120 mm Hg and heart rate 105 beats/minute. She states that she felt a little lightheaded but that she now feels okay. She ran out of her blood pressure medications (including hydrochlorothiazide, carvedilol, and lisinopril) 3 days ago. Her current laboratory values are within normal limits. Which medication is best for this patient?
- A. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
  - B. Labetalol 80 mg intravenously; repeat until blood pressure is less than 120/80 mm Hg.
  - C. Resumption of home medications; refer for follow-up within 2 days.
  - D. Resumption of home medications; initiate amlodipine 10 mg daily; refer for follow-up in 1 week.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: A**

This patient's atypical symptoms, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTEMI-ACS. She has at least three risk factors for CAD, a history of CAD (prior MI), and positive troponins, which place her at high risk of future events. In such high-risk patients, an early invasive strategy (as in Answers A and B) is used to determine whether occluded or partly occluded arteries exist, which ones can be intervened on, and whether to make an intervention. An ischemia-guided approach, also called "medical management," as in Answers C and D, would not be preferred because of this patient's risk category (i.e., positive troponins). Dual antiplatelet therapy (aspirin plus a P2Y<sub>12</sub> inhibitor) is indicated for an early invasive strategy in managing an NSTEMI-ACS. In patients undergoing PCI, clopidogrel, prasugrel, or ticagrelor is appropriate (Answer A is correct). After an initial bolus of 60 units/kg and an infusion of 12 units/kg/hour (Answer A is correct; Answer D is incorrect), UFH can be titrated to an aPTT of 50–70 seconds. Aspirin alone without a P2Y<sub>12</sub> agent, as in Answer B, would not provide adequate antiplatelet therapy. Furthermore, enoxaparin would need to be dosed with a 30-mg intravenous bolus before initiating twice-daily subcutaneous dosing because this patient has positive troponins. Glycoprotein IIb/IIIa inhibitors, as in Answer C, can be useful in high-risk patients, typically those with positive troponins; however, their benefit has been shown mainly when UFH, not low-molecular-weight heparin, is given as the anticoagulant.

**2. Answer: C**

Of importance, this patient case occurs in the context of elective stent placement, not after ACS. In the non-ACS setting, the duration of DAPT is determined by the type of stent placed (bare metal stent vs. drug-eluting stent). After elective drug-eluting stent placement, DAPT is recommended for at least 6 months because the risk of in-stent thrombosis is highest during this time (Answer C is correct). The recommendation is for at least 1 month after bare metal stent placement because endothelialization of the stent usually occurs early, typically within 1 month after stenting (Answer A is incorrect). Bleeding risk may be a reason to consider earlier termination (after at least 1 month) of DAPT after bare metal stent placement. Although European guidelines

consider 3 months of DAPT after drug-eluting stent placement appropriate, the recommended minimum according to the U.S. guidelines is 6 months (Answer B is incorrect). Twelve months of therapy is recommended after ACS (Answer D is incorrect).

**3. Answer: D**

Because the patient presents to a hospital that can do a primary PCI with stent implantation, this is the preferred reperfusion strategy (Answers B and C are incorrect). Answer A is incorrect because an anticoagulant agent must be administered in addition to antiplatelet therapy. Reperfusion with fibrinolytic therapy (Answers B and C) would only be considered if PCI were expected to be delayed by more than 120 minutes. In addition, Answer C is incorrect because bivalirudin has not been studied with lytic therapy. Answer D – reperfusion with primary PCI, DAPT with aspirin and prasugrel, and dosing of bivalirudin as an anticoagulant strategy – is correct.

**4. Answer: C**

Unlike the patient in case 3, this patient presents with a STEMI to a rural community hospital where the nearest hospital with catheterization laboratory facilities is more than 120 minutes away (i.e., lytics are indicated). He presents within the window for fibrinolytic therapy consideration (less than 6 hours after chest pain onset) and has no obvious contraindications. Because he is still having ischemic chest pain and ST-segment elevation, he should benefit from reperfusion therapy. He is experiencing bradycardia, which could indicate an occlusion above the area perfusing his sinoatrial or atrioventricular nodes. Enoxaparin is a treatment option for anticoagulant therapy given in conjunction with fibrinolytics, but the patient is at higher risk of bleeding from impaired enoxaparin clearance and needs a dosage adjustment. Furthermore, he is older than 75, beyond the age at which the intravenous bolus should be given, and the alteplase dosing is incomplete (Answer A is incorrect). Simply treating this patient conservatively with UFH alone in the setting of ongoing chest pain, shortness of breath, and pulmonary edema is not optimal (Answer B is incorrect). Diagnostic catheterization and possible PCI to determine whether an artery can be reperfused may be desirable but is complicated because the patient's SCr is elevated (2.5 mg/dL), and he is in a rural hospital, where he cannot be assessed

quickly enough (within 90–120 minutes) (Answer D is incorrect). Because of the shorter half-life and ease of administration of tenecteplase, tenecteplase may be preferable to alteplase. Clearance of UFH with tenecteplase is not as altered as with enoxaparin, and it would be a more appropriate therapy than enoxaparin in combination with a thrombolytic (Answer C is correct).

**5. Answer: C**

This patient, who has ADHF, is receiving a  $\beta$ -blocker. Although long-term  $\beta$ -blockers can improve HF symptoms and reduce mortality, they can also worsen symptoms in the short term. It is recommended to keep the maintenance  $\beta$ -blocker therapy at the same or at a slightly lower dose compared with the outpatient therapy in patients with ADHF; increasing the  $\beta$ -blocker dose before reaching euvolemia might acutely worsen his clinical picture (Answer A is incorrect). In patients admitted with volume overload without substantial signs of reduced CO, it is reasonable to try intravenous loop diuretics initially (Answer C is correct). As gut edema increases, oral loop diuretics (notably furosemide) become less effective because of decreased absorption. Sodium nitroprusside could be useful if signs and symptoms of hypoperfusion were present. Because this patient presents mainly with warm and wet symptoms, diuretics would be first-line (Answer B is incorrect). Milrinone is an inotropic drug. Because of their adverse effects, inotropes are recommended in cold and wet exacerbations only after vasodilatory medications have failed (Answer D is incorrect).

**6. Answer: A**

Intravenous vasodilators such as nitroglycerin (Answer A) and sodium nitroprusside (Answer B) are reasonable if intravenous diuretics fail and the patient progresses to acute pulmonary edema. Both agents rapidly cause venous vasodilation and reduce pulmonary filling pressures, which can relieve acute shortness of breath. Answer A, nitroglycerin, is optimal for this patient, given his declining renal function and the concern for increased risk of thiocyanate toxicity with sodium nitroprusside in this setting (Answer B is incorrect). Dobutamine is typically used in states of low CO decompensation and is counteracted by concomitant  $\beta$ -blocker therapy, making it a poor choice in patients receiving  $\beta$ -blockers (Answer C is incorrect). Although milrinone is a more acceptable inotropic agent in a

patient receiving  $\beta$ -blockers, the dosing strategy is inappropriate as an initial dose (Answer D is incorrect). Finally, inotropes are generally reserved for patients when other therapies have failed.

**7. Answer: A**

Signs of a decreased CO state in HF (e.g., increased SCr, decreased mental status, cool extremities) suggest a cold and wet state, and adjunctive therapy is indicated. Positive inotropic agents such as milrinone will increase CO to maintain perfusion to vital organs. Milrinone will also vasodilate the peripheral vessels to unload the heart (lower SVR). Although dobutamine would be a potential choice in this patient, it is not recommended in patients receiving  $\beta$ -blockers, and the initial starting dose is too aggressive (Answer B is incorrect). Although this patient has low blood pressure, his elevated SVR suggests that he will tolerate the vasodilatory effects of milrinone as long as it is appropriately renally adjusted for worsening renal dysfunction (Answer A is correct). Nitroprusside would be relatively contraindicated in patients with an SBP less than 100 mm Hg and is absolutely contraindicated in patients with an SBP less than 90 mm Hg (Answer C is incorrect). Phenylephrine has no positive beta effects; therefore, it will not augment contractility. In addition, it will cause vasoconstriction through alpha stimulation, which will further increase SVR and probably worsen CO (Answer D is incorrect). Vasoconstrictors are reserved for patients in cardiogenic shock.

**8. Answer: A**

Treatment options for sustained VT depend on concomitant disease states, particularly LVEF (40% cutoff). In a patient with LV dysfunction, class I agents such as procainamide are contraindicated (Answer D is incorrect). In a patient whose CrCl is less than 60 mL/minute, sotalol requires a considerable dose reduction to avoid an excess risk of torsades de pointes. Sotalol is not an effective cardioversion drug but is more useful for preventing future episodes of arrhythmias (maintaining sinus rhythm) once sinus rhythm is achieved (Answer B is incorrect). Dofetilide is indicated only for AF, not for ventricular arrhythmias; similarly, cardioversion rates with dofetilide are low (Answer C is incorrect). Amiodarone is first-line therapy for sustained VT in patients with severe renal insufficiency, HF, and SHD (Answer A is correct).

**9. Answer: C**

With the prolonged half-life of amiodarone and extensive fat tissue volume of distribution, hyperthyroid adverse effects would be expected to last for 3–5 half-lives of the drug, which is 5–8 months (Answer C is correct; Answer A is incorrect). Although therapeutic concentrations may decrease substantially by then, 1 month is too soon for the effects to subside (Answer B is incorrect). Although some iodine and amiodarone molecules will probably remain absorbed in fat stores for years, if not for life, therapeutic concentrations should not exist for longer than what is predicted by the half-life (Answer D is incorrect).

**10. Answer: D**

This patient is having QT prolongation with sotalol, placing her at an elevated risk of developing life-threatening torsades de pointes. Sotalol should be discontinued immediately (Answers A and B are incorrect). Given the QT prolongation that occurred with sotalol, the same will probably occur with dofetilide (Answer C is incorrect). Amiodarone is associated with minimal risk of torsades de pointes and therefore would be an appropriate alternative agent to prevent ventricular arrhythmias (Answer D is correct).

**11. Answer: A**

Hypertensive emergency should be treated immediately by no more than a 25% reduction in MAP over the first hour, followed by a further reduction to a blood pressure of 160/100 mm Hg over the next 2–6 hours. The patient's comorbidities guide the optimal therapy. His dialysis and SCr of 11.4 mg/dL are contraindications to sodium nitroprusside (Answer C is incorrect) because of possible thiocyanate toxicity. Labetalol (and  $\beta$ -blockers in general) is controversial in patients who have taken cocaine, but its nonselective nature makes it an option; however, a reduction of 50% initially is too rapid a decrease in blood pressure for safety (Answer B is incorrect). Clonidine is not appropriate for a hypertensive emergency because its oral form is difficult to titrate and can lead to precipitous drops in blood pressure beyond the goal 25% reduction and possibly stroke or worsening MI (Answer D is incorrect). Nitroglycerin is optimal, considering the patient's lack of contraindications to this therapy and his evolving MI and symptoms of HF (Answer A is correct).

**12. Answer: C**

In an asymptomatic hypertensive crisis (without acute target-organ damage), giving intravenous medications, as in Answers A and B, and admitting the patient to the hospital are unnecessary (Answers A and B are incorrect). This patient is likely presenting because of recent nonadherence. Resuming her home medications (Answer C is correct) at this time would be most appropriate, with a close follow-up to ensure that her prescribed regimen is working. Adding a fourth agent (Answer D is incorrect) at this time is unnecessary, considering that her disease could be controlled on her current drug regimen if she were adherent. Follow-up should occur within the first few days, rather than waiting 1 week.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

This patient's chest pain, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTEMI-ACS. Because of his presentation characteristics, he is at a high enough risk to warrant cardiac catheterization (invasive strategy). This invasive strategy is used to determine whether occluded or partly occluded epicardial arteries exist, which ones can be intervened on, and whether to do PCI (percutaneous transluminal coronary angioplasty with or without stenting). Initial therapy for ACS usually consists of morphine, oxygen, nitroglycerin, and aspirin, but only aspirin has been shown to reduce mortality from these initial treatments. Aspirin should be given as soon as possible after hospital presentation and continued indefinitely, if tolerated. According to clinical trials, guidelines, and experience, an initial dose of 162–325 mg is recommended (Answers B and D are not the best choices of dosing for an acute episode). Aspirin, together with a P2Y<sub>12</sub> receptor antagonist, is indicated for an early invasive strategy in the management of UA/NSTEMI, improving outcomes. The 2014 NSTEMI-ACS guidelines give a class I recommendation for clopidogrel, ticagrelor, and prasugrel in ACS for patients undergoing PCI. The choice of which P2Y<sub>12</sub> receptor antagonist to use in the ACS setting depends on patient presentation, contraindications, and whether PCI is involved; in this case, any of the three P2Y<sub>12</sub> antagonists would be appropriate. The anticoagulation strategy treatment for ACS generally includes one anticoagulant (UFH, low-molecular-weight heparin, fondaparinux, or bivalirudin). When UFH is chosen as an anticoagulant strategy, the dose used for ACS is a 60-unit/kg bolus and a 12-unit/kg/hour infusion (Answer A is incorrect). Regarding dosing, bivalirudin (Answer D) would be an appropriate anticoagulation strategy; however, the initial aspirin dose should be higher, and a nitroglycerin drip would not be the best choice, given his right-sided MI (low blood pressure, low heart rate). Answer A is reasonable in patients without contraindications when hypertension or ongoing ischemia is a concern; however, initiating oral therapy within 24 hours is preferred in most patients as long as they have no signs of HF, evidence of low output state, increased risk of cardiogenic shock, or other contraindications to  $\beta$ -blockade.  $\beta$ -Blockers should initially be avoided in this patient, given his blood pressure and decreased baseline heart

rate. An intravenous ACE inhibitor (Answer B) should not be given to patients within the first 24 hours of ACS because of the increased risk of hypotension. Answer C includes DAPT and an appropriate anticoagulant dose (Answer C is correct).

**2. Answer: A**

The NSTEMI-ACS guidelines recommend the use of one anticoagulant during an acute event. Enoxaparin, UFH, and bivalirudin are all recommended as class I agents for the invasive management of NSTEMI-ACS. However, fondaparinux (Answer C) is not optimal because of the increased risk of catheter-related thrombosis associated with its use in the catheterization laboratory. The NSTEMI-ACS guidelines advise the use of an additional anticoagulant with class IIa activity (heparin or bivalirudin) if fondaparinux was an initial anticoagulant when the patient underwent intervention, whereas the PCI guidelines give fondaparinux a class III or harmful recommendation. Of the remaining three options, UFH (Answer A) is preferred because of its dosage and rapid clearance regardless of renal function. The UFH bolus should be limited to 4000 units, and the initial infusion should be limited to 1000 units/hour. Both enoxaparin (Answer B) and bivalirudin (Answer D) would be appropriate but would need to be dose adjusted, given this patient's CrCl of less than 30 mL/minute. However, the doses in Answers B and D would be appropriate for patients with a normal CrCl.

**3. Answer: B**

An anticoagulant is required for PCI. Options include UFH, bivalirudin, and enoxaparin. Because this patient had a significantly low Plt with his most recent heparin exposure and was confirmed to have HIT, using any of the GP IIb/IIIa inhibitors (Answers A and C) would be unwise for ACS treatment because these agents are usually combined with UFH. Furthermore, GP IIb/IIIa inhibitors are antiplatelets, and the patient will still need an additional agent with anticoagulant activity. Thrombolytic therapy is not recommended for NSTEMI-ACS and would be inappropriate in this patient (Answer D is incorrect). Answer D is also incorrect because enoxaparin carries a 10% risk of cross-reactivity if HIT is suspected. Bivalirudin (Answer B), a direct thrombin inhibitor, would be the treatment of choice in patients with HIT undergoing PCI.

**4. Answer: D**

$\beta$ -Blocker therapy can cause HF decompensation, particularly when the  $\beta$ -blocker is titrated too quickly or initiated in patients who are not euvolemic. Although administering  $\beta$ -blockers within the first 24 hours is beneficial in STEMI, this patient has several risk factors that would be considered contraindications to initial  $\beta$ -blockade. This patient's clinical condition suggests he is not euvolemic, and aggressive diuresis should be tried before a  $\beta$ -blocker is initiated for him. In addition, intravenous  $\beta$ -blocker therapy (Answer B) would place him at an even greater risk of cardiogenic shock. Answers A and C are inappropriate because the doses are fairly aggressive for a patient with an EF of 25% and marginal blood pressure. Answer D is correct; however, before discharge, this patient should be reevaluated for the initiation of low-dose  $\beta$ -blocker therapy.

**5. Answer: B**

Dual antiplatelet therapy is recommended for at least 12 months in patients presenting with ACS. Early discontinuation of DAPT is reasonable when the risk of morbidity exceeds the expected benefit (class IIa), as in the case of bleeding. Answers C and D do not represent the minimum time interval, given that the patient has no known risk of bleeding. Prasugrel (Answer B) would be preferable to clopidogrel (Answer A) in this scenario because it would be faster in onset; clopidogrel would take about 6 hours for maximal platelet inhibition after a 300-mg LD. Subgroup analysis of a randomized placebo-controlled trial comparing the effectiveness of prasugrel and clopidogrel showed the superiority of prasugrel, especially for patients presenting with a STEMI (Answer B is correct).

**6. Answer: C**

This patient is well perfused and can be classified in Forrester hemodynamic subset II (warm and wet). Because the patient has pulmonary congestion (shortness of breath, dyspnea at rest), intravenous diuretics are first-line therapy. Nitroglycerin (Answer C) is best in this setting because vasodilatory agents can be used in conjunction with intravenous diuretics to improve acute pulmonary edema. When adjunctive therapy is needed in addition to loop diuretics, intravenous vasodilators should be considered over inotropic agents when blood pressure is adequate. Dobutamine (Answer A) and milrinone (Answer B) primarily increase CO, which is not a problem in warm and wet exacerbations. In addition, the adverse effects of these agents (increased mortality,

proarrhythmia) limit their use. Intravenous metoprolol (Answer D) should be used extremely cautiously because of its negative inotropic effects and because this patient is not in a euvolemic state.

**7. Answer: D**

This patient has a depressed LVEF less than 40%; therefore, her AAD therapy options are limited. Procainamide (Answer A) is indicated only in secondary prevention of sustained VT in patients with a normal LVEF greater than 40%; if given to this patient, it could worsen her HF. Metoprolol (Answer B) is indicated for treating patients with asymptomatic nonsustained VT and SVT associated with CAD. This patient had an episode of sustained VT; therefore, therapy beyond  $\beta$ -blockade is warranted. Her QTc interval is not prolonged at 380 milliseconds, and her serum magnesium concentration is within normal limits; thus, she does not need intravenous magnesium therapy (Answer C). Amiodarone (Answer D) is first line for patients without contraindications because of its efficacy and safety in patients with an LVEF less than 40%.

**8. Answer: B**

This patient has target-organ damage from poorly controlled hypertension in the form of retinal hemorrhaging. Fenoldopam is contraindicated for treating hypertensive emergencies in the setting of glaucoma (Answer A is incorrect). Nicardipine is appropriate for this patient, given the details of this case (Answer B is correct). Although labetalol is effective for treating hypertensive emergency, this patient has a history of asthma and a low heart rate, making labetalol a less-than-ideal option for treating her symptoms (Answer C is incorrect). The antihypertensive effects of enalaprilat depend on a patient's renin activity, which is unknown in this case. Therefore, the blood pressure-reducing effects may be more difficult to control than when using a drug having a more consistent effect in individuals. In addition, the bolus nature of the drug is not ideal for tightly controlling blood pressure with no more than a 25% reduction in MAP. Continuous infusion drugs are preferable for easier titration to effect in a hypertensive emergency (Answer D is incorrect).

**9. Answer: C**

The Cardiac Arrest Study Hamburg trial compared ICD with AAD in survivors of cardiac arrest for secondary prevention of SCD. The propafenone (Answer A) study

arm was discontinued early because of its significantly (61%) higher mortality rate compared with the ICD arm (Answer A is incorrect). Although this trial had a small sample size that prevented a statistically significant difference in total mortality in ICD-treated patients versus patients treated with either amiodarone or metoprolol, the incidence of sudden death was significantly lower in patients with an ICD (Answer C is correct; 33% vs. 13%;  $p=0.005$ ). The Antiarrhythmics Versus Implantable Defibrillators trial also evaluated ICD implantation versus AAD therapy (primarily amiodarone) in survivors of SCD. Patients with ICDs had a significantly higher rate of survival than did those treated with drug therapy (89% vs. 82%;  $p<0.02$ ), making Answer C preferable to all the other options (Answers B and D are incorrect).

#### 10. Answer: C

The number needed to treat can be calculated as  $1/\text{absolute risk reduction}$ . Because the absolute risk reduction in mortality at 60 months was 7.2% with ICD versus placebo,  $1/0.072$  would be used to calculate the number of patients needed to treat to prevent one death during this time. About 14 patients (Answer C) would need to be treated with ICD to prevent one death in 60 months versus placebo. Other calculations in this fashion, including relative risk reduction and 100% minus the absolute or relative risk reduction, provide no useful information for interpreting the trial results and yield an incorrect number of patients (Answers A, B, and D are incorrect).

#### 11. Answer: D

International Pharmaceutical Abstracts (Answer A) is a database of primarily pharmaceutical abstracts in more than 750 journals, including foreign and state pharmacy journals, in addition to key U.S. medical and pharmacy journals. Many of the citations are not included on Medline, so a broader search can be done; however, subject descriptors are not consistently defined in a uniform way, and multiword terms are often cited backward. The Iowa Drug Information Service database (Answer B) offers full-text articles from 1966 to the present in about 200 medical and pharmacy journals (based primarily in the United States). This database is updated monthly, and newly available articles may take longer to access from this service. The Clin-Alert database (Answer C) contains more than 100 medical and pharmacy journals focused on adverse events, drug interactions, and medical-legal issues. This database is used primarily to look up adverse events (especially recent

reports) associated with medications. Excerpta Medica (Answer D) is a comprehensive database of more than 7000 journals from 74 countries dating from 1974 to the present. Recently published articles appear in the system within 10 days of article publication, and it often contains data not found in a typical Medline search.

#### 12. Answer: B

MedWatch is a post-FDA approval program established by the FDA for health care professionals to report the adverse events that occur after a drug is approved. Although MedWatch is commonly used only for reporting serious reactions to the FDA and would not be mandatory in this case (Answer A is incorrect), it can be used to report any adverse event. Information recorded on these forms is reported to the manufacturer and used to determine whether black box warnings are necessary or whether new adverse effects occur with a drug. The Joint Commission requires that all institutions have a definition of an ADR that can be understood and remembered by all health care professionals at the institution (Answer B is correct). In addition, The Joint Commission requires that each drug dose administered be monitored for adverse effects, that each institution have a system in place for reporting ADRs, and that the institution ensure that the reporting mechanism identifies all key ADRs. The Naranjo algorithm is used to determine the likelihood of cause and effect from a presumed drug-induced event but is not required (Answer C is incorrect). Answer D is incorrect because serious adverse effects are reportable to the FDA, as are severe and life-threatening events.

#### 13. Answer: B

Because the pharmacy and therapeutics committee wants to discover whether the new drug is worth the extra cost for the added mortality benefits it can provide for patients with decompensated HF compared with available therapies, a cost-effectiveness analysis (Answer B is correct) is the best pharmacoeconomic analysis. Cost-minimization analysis (Answer A is incorrect) determines whether a therapeutically equivalent drug within a class that provides the same therapeutic outcome as other available drugs can be used for less cost. Cost-utility analysis (Answer D is incorrect) determines whether a drug can improve the quality of a patient's life more than other available therapies. Cost-benefit analysis (Answer C is incorrect) evaluates new programs or services to determine whether they provide enough benefit to justify their cost.