

CRITICAL CARE
SELF-ASSESSMENT PROGRAM

CCSAP



2017 • BOOK 1

**CARDIOLOGY
CRITICAL CARE**

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AMERICAN COLLEGE OF CLINICAL PHARMACY

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Critical Care
Self-Assessment
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Message from the Editors

Welcome to the Critical Care Self-Assessment Program (CCSAP), a new recertification component for the Board Certified Critical Care Pharmacist. ACCP has a long tradition of offering the best products for continuing pharmacy education and pharmacotherapy specialist certification. CCSAP continues that tradition by providing the latest in evidence-based information for the critical care practitioner or clinician.

In designing this series, the primary goal was to provide updates that would improve clinical pharmacy practice and patient outcomes. The process began with a careful review of the content outline developed by the Board of Pharmacy Specialties for the Critical Care Pharmacy Specialty Certification Examination. The 2017–2018 CCSAP chapters will therefore cover the domains of clinical skills and therapeutic management; practice administration and development; and information management and education. Specific content for individual releases in this series was organized on the basis of the systems and patient care problems that might be expected of the board certified critical care pharmacy specialist. Finally, calls went out to recruit faculty panel

chairs, authors, and reviewers committed to this new specialty and to the board certification process.

The presentation of information, and its incorporation into practice, was also given careful consideration. Inside this CCSAP book, you will find user-friendly formatting as well as graphic elements such as patient care scenarios demonstrating the application of concepts, treatment algorithms, descriptions of pivotal studies that may change practice, and summative practice points. All releases in this series are available electronically, enhancing the portability of this product. Prominent in each chapter are hyperlinks to reference sources, assessment tools, guidelines and resources, data compilers such as PubMed, and even informational videos. Our hope is that this depth of information, ease of access, and emphasis on clinical application will have an immediate and positive impact on the care of patients in the ICU and other critical care settings.

We very much appreciate the efforts of all the contributors who lent their energy and expertise to this new series.

Bradley A. Boucher and Curtis E. Haas, series editors

Cardiology Critical Care I

Cardiology Critical Care I Panel

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Antithrombotic Therapies in Acute Coronary Syndrome

By Steven P. Dunn, Pharm.D., FAHA, BCPS-AQ Cardiology; and Hasan Kazmi, Pharm.D., BCPS

Reviewed by Paul P. Dobesh, Pharm.D., FCCP, BCPS-AQ Cardiology; and Ola Adejuwon, Pharm.D., BCPS, BCCCP, BCNSP

LEARNING OBJECTIVES

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

ABBREVIATIONS IN THIS CHAPTER

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

[*Table of other common abbreviations.*](#)

INTRODUCTION

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

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

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

Objective markers of myocardial necrosis, such as cardiac biomarkers, are also difficult to interpret in critically ill patients. Plasma troponin concentration, a standard for the diagnosis of MI, is unreliable in critically ill patients because of the assay's extreme sensitivity in distinguishing myocardial ischemia caused by coronary thrombosis from a wide range of pathologies. More than 60% of critically ill patients may have a detectable plasma troponin concentration (Hamilton 2012). Transient cardiac biomarkers in critically ill patients can greatly confuse the specific diagnosis and cause harm from misapplied therapies. For example, one group of investigators identified that of 171 patients

admitted to an ICU, 42.1% had elevated troponin I concentrations, but only 22.2% of all patients had an MI (Lim 2006). To this end, key stakeholders from leading cardiovascular societies in the United States and worldwide have developed a universal definition of MI to delineate the specific causes of myocardial ischemia, which is now in its third iteration (Table 1-1).

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

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General treatments and approaches to the management of acute coronary syndrome
- Coronary and cardiac anatomy and physiology
- Pharmacologic properties of various anticoagulant and antiplatelet therapies

Table of common laboratory reference values.

ADDITIONAL READINGS

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

TREATMENT STRATEGIES FOR ACS IN CRITICALLY ILL PATIENTS

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

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

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

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

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

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

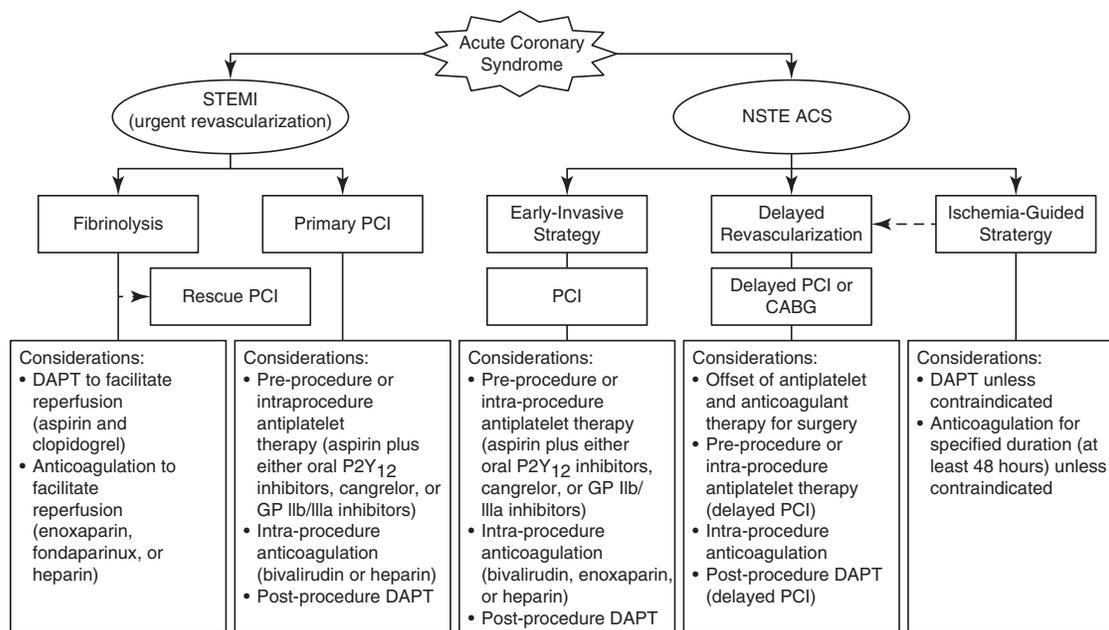


Figure 1-1. Antiplatelet and antithrombotic therapy for acute coronary syndrome. This figure depicts general recommendations for the two major strata of acute coronary syndrome regarding antiplatelet and antithrombotic therapy. Usefulness and duration of antiplatelet therapy depend greatly on the modality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

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

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

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Fibrinolysis

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

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

Dual antiplatelet therapy (DAPT) is also indicated for patients receiving fibrinolytic therapy for STEMI. Aspirin reduced vascular mortality in combination with streptokinase in the ISIS-2 trial (ISIS-2 Collaborative Group 1988). In CLARITY, use of clopidogrel in addition to aspirin and standard fibrinolytic therapy was associated with greater arterial patency and reduced 30-day adverse cardiovascular outcomes compared

with placebo. In addition, 30-day mortality was reduced with DAPT (Sabatine 2005). No data exist with newer P2Y₁₂ inhibitors for fibrinolytic therapy. Therefore, the choice of P2Y₁₂ inhibitor for fibrinolysis should be limited to clopidogrel at a loading dose of 300 mg, followed by 75 mg daily; patients older than 75 should receive 75 mg daily only because of their exclusion in CLARITY and concern for greater risk of bleeding.

Primary PCI

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

Pre-procedure

Pre-procedural antithrombotic therapy is largely used with the goals of successful clot stabilization and facilitation of intra-procedural success. Aspirin therapy (81–325 mg) is the recommended initial treatment for all phases of ACS, including STEMI, as well as before cardiac catheterization (Amsterdam 2014). This provides a baseline level of platelet inhibition and generally has been included as part of PCI procedures since their inception. In critically ill patients, non-enteric-coated aspirin products, ideally crushed, are recommended either orally or through feeding tubes because of their superior onset of action. If oral access is not available, aspirin suppositories can be considered, though they are less preferable, given the significant delay (up to 4 hours) in onset of action compared with crushed oral dosage forms. Using pre-procedural P2Y₁₂ inhibition to more completely inhibit platelet-driven thrombosis is controversial. Although this "preloading" is generally thought to facilitate PCI efficacy and is guideline recommended, the superiority of earlier P2Y₁₂ inhibition has

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

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

^aWith planned readministration of streptokinase.

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

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

not been conclusively proven by a well-designed trial, even with use of a faster-acting oral P2Y₁₂ inhibitor. Cangrelor, an intravenous P2Y₁₂ inhibitor with rapid onset and a significantly shortened half-life, is an attractive alternative to oral agents in the pre-procedural STEMI setting. Unfortunately, all evidence to date for cangrelor has focused on the intra- and post-procedural settings. In addition, recovery of platelet function after receiving oral P2Y₁₂ inhibitor therapy occurs over a minimum of several days, regardless of drug choice. This presents challenges if the patient requires urgent surgical revascularization because performing surgery under the exposure of these agents increases surgical complications.

However, patients with STEMI rarely (less than 5% of cases) undergo surgical revascularization (Gu 2010). Gastric access is required for P2Y₁₂ inhibitors; no experience with alternative dosage forms exists, though crushed dosage forms appear to confer faster pharmacodynamic onset, leading to reduced platelet reactivity compared with whole tablets as soon as 30 minutes post-dose with prasugrel (Rollini 2016).

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

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

Intra-procedure

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

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

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

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

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Mechanism of Action	AT-mediated inhibition of factors II and X	AT-mediated inhibition of factors X > II	AT-mediated inhibition of factor X	Direct thrombin (II) inhibitor
Dosing	<p>Fibrinolysis, NSTEMI ACS, or ischemia-guided therapy:</p> <ul style="list-style-type: none"> • 60 unit/kg bolus (max 4000 units) + 12 units/kg/hr infusion (initial max 1000 units/hr), titrated to therapeutic aPTT for 48 hr or until revascularization <p>PCI with planned GPI:</p> <ul style="list-style-type: none"> • 50–70 units/kg IV bolus to achieve therapeutic ACT <p>PCI without planned GPI:</p> <ul style="list-style-type: none"> • 70–100 units/kg IV bolus to achieve therapeutic ACT 	<p>Fibrinolysis:</p> <ul style="list-style-type: none"> • ≤ 75 yr: 30 mg IV bolus, then 15 min later 1 mg/kg SC q12hr (max 100 mg for first two doses, give first dose with initial IV dose) • >75 yr: No bolus, 0.75 mg/kg SC q12hr (max 75 mg for first two doses) • CrCl < 30 mL/min/1.73 m²: 30 mg IV bolus (omit if > 75 yr) and 1 mg/kg SC q24hr (give first dose with initial IV dose with max of 100 mg) <p>Duration is for index hospitalization up to 8 days, or until revascularization</p> <p>NSTEMI ACS/ischemia-guided therapy:</p> <p>1 mg/kg SC q12hr for duration of hospitalization or until revascularization</p> <p>Primary PCI:</p> <ul style="list-style-type: none"> • 0.5–0.75 mg/kg IV bolus if no anticoagulation previously • 0.3 mg/kg IV if last SC dose was > 8 hr before PCI, or only one SC dose given 	<p>Fibrinolysis:</p> <ul style="list-style-type: none"> • 2.5 mg IV x 1, then 2.5 mg SC daily starting the next day for index hospitalization up to 8 days, or until revascularization <p>NSTEMI ACS/ischemia-guided therapy:</p> <ul style="list-style-type: none"> • 2.5 mg SC daily for duration of hospitalization or until revascularization <p>PCI:</p> <ul style="list-style-type: none"> • Not recommended without additional anticoagulant with anti-II activity 	<p>ACS:</p> <ul style="list-style-type: none"> • 0.15–2 mg/kg/hr infusion, titrated to aPTT goal <p>PCI:</p> <ul style="list-style-type: none"> • 0.75 mg/kg IV bolus + 1.75 mg/kg/hr infusion
Monitoring	aPTT, anti-Xa, and/or ACT (200–250 s during PCI with GPI or 250–300 s without GPI), Hgb, Hct, Plt	Renal function, Hgb, Hct, Plt, anti-Xa (as indicated)	Renal function, Hgb, Hct	PTT and/or ACT as indicated, renal function, Hgb, Hct
Onset	Immediate	IV: Immediate SC: 2 hr	IV: Immediate SC: 2 hr	Immediate
Duration	1–2 hr	IV: 6 hr SC: 12 hr (longer with renal dysfunction)	17–21 hr (longer with renal dysfunction)	1–3 hr based on renal function

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

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

Study (yr)	Pertinent Inclusion/Exclusion Criteria	Intervention/Methods	End Points	Pertinent Baseline Characteristics	Outcomes
ACUITY (2006)	Incl.: NSTEMI ACS Excl: STEMI	Three arms: 1) UFH or enoxaparin + GPI 2) Bivalirudin + GPI 3) Bivalirudin alone ± bailout GPIIb/IIIa	<ul style="list-style-type: none"> • Composite of death, MI, unplanned revascularization • Major bleeding • Net benefit (composite + major bleeding) 	n=13,189 NSTEMI 59%, UA 41% PCI 55% ASA 98%, clopidogrel 63% Radial access: Arm 1: 47% UFH, 47% enoxaparin	<ul style="list-style-type: none"> • Arm 2 vs. 1: noninferior in composite, major bleeding, and net clinical outcome • Arm 3 vs. 1: noninferior in composite; superior in bleeding (3.0% vs. 5.7%, RR 0.53, p<0.001) and net clinical outcome (10.1% vs. 11.7%, RR 0.86, p=0.015)
HORIZONS-AMI (2008)	Incl: STEMI Excl: NSTEMI ACS	Two arms: 1) UFH + universal GPI 2) Bivalirudin + provisional GPI	<ul style="list-style-type: none"> • Major bleeding • Net adverse clinical events (major bleeding or MACE) 	n=3602 GPI use in 7.2% of bivalirudin arm, clopidogrel 98%	<ul style="list-style-type: none"> • Major bleeding: bivalirudin 4.9% vs. 8.3%, RR 0.60 (p<0.002) • Net events: 9.2% vs. 12.1%, RR 0.76 (p=0.005) • All-cause mortality: 2.1% vs. 3.1%, RR 0.66 (p=0.047) • Acute stent thrombosis: 1.3% vs. 0.3%, RR 4.3 (p<0.001)
ISAR-REACT 4 (2011)	Incl: NSTEMI with definite planned PCI Excl: STEMI, UA	Two arms: 1) UFH + abciximab 2) Bivalirudin	<ul style="list-style-type: none"> • Composite of death, large recurrent MI, urgent TVR, major 30-day bleeding • Major bleeding 	n=1721 88% DES 99% femoral access	<ul style="list-style-type: none"> • No difference in composite outcome • Major bleeding UFH 4.6% vs. 2.6%, RR 1.84 (p=0.02)
EUROMAX (2013)	Incl: STEMI Excl: NSTEMI ACS	Two arms: 1) Bivalirudin + provisional GPI+ post PCI bivalirudin x 4 hr 2) UFH/ enoxaparin + provisional GPI	<ul style="list-style-type: none"> • Composite: death or major non-CABG bleeding • Net events (MACE + non-CABG bleeding) 	n=2218 Clopidogrel 40%, prasugrel 30%, ticagrelor 30% UFH 90%, enoxaparin 8.5% GPI use: 11.5% vs. 69% Radial access: 46%	<ul style="list-style-type: none"> • Composite: bivalirudin 5.1% vs. 8.5%, RR 0.60 (p=0.001) • MACE: 6.0% vs. 5.5%, RR 1.09 (p=0.64) • Net events: 6.6% vs. 9.2%, RR 0.72 (p=0.02) • Major bleeding: 2.6% vs. 6.0%, RR 0.43 (p<0.001) • Acute stent thrombosis: 1.1% vs. 0.2%, RR 6.11 (p=0.007)
HEAT-PPCI (2014)	Incl: STEMI	Two arms: 1) Bivalirudin (provisional GPI allowed) 2) UFH (provisional GPI allowed)	<ul style="list-style-type: none"> • MACE (death, CVA, reinfarction, unplanned revascularization) • Major bleeding 	n=1812 Clopidogrel 11%, prasugrel 28%, ticagrelor 62% Radial access 80% GPI: UFH group 15% vs. bivalirudin group 13%	<ul style="list-style-type: none"> • MACE: Bivalirudin 8.7% vs. 5.7%, RR 1.54 (p=0.01) • Major bleeding: 3.5% vs. 3.1% (p=0.59)
BRAVE-4 (2014)	Incl: STEMI	Two arms: 1) Bivalirudin + prasugrel (provisional GPI allowed) 2) UFH + clopidogrel (provisional GPI allowed)	<ul style="list-style-type: none"> • Composite: death, MI, unplanned revascularization, stent thrombosis, stroke, major bleeding 	Trial stopped early for low recruitment n=548 GPI use: Bivalirudin 3.0% vs. UFH 6.1% Femoral access: 99%	<ul style="list-style-type: none"> • Composite: Bivalirudin 15.6% vs. 14.5% (p=0.680) • Bleeding: 14.1% vs. 12.0% (p=0.543)

(Continued)

Table 1-4. (Continued)

Study (yr)	Pertinent Inclusion/Exclusion Criteria	Intervention/Methods	End Points	Pertinent Baseline Characteristics	Outcomes
MATRIX (2015)	Incl: STEMI or NSTEMI; PCI candidate	Two arms: 1) Bivalirudin + provisional GPI (group subsequently randomized to receive post PCI bivalirudin x 4 hr vs. placebo) 2) UFH + provisional GPI	<ul style="list-style-type: none"> • MACE: Composite of all-cause death, MI, stroke up to 30 days • Net events: Major non-CABG bleeding + MACE up to 30 days • Post-PCI infusion outcome: Composite of urgent TVR, definite stent thrombosis, or net adverse clinical events up to 30 days 	n=7213 Clopidogrel 46%, prasugrel 24%, ticagrelor 13% GPI use: 4.6% vs. 26% Radial access: 50%	<ul style="list-style-type: none"> • MACE: bivalirudin 10.3% vs. 10.9% (p=0.44, note: UFH + <i>planned</i> GPI rate was 8.1%) • Net events: 11.2% vs. 12.4% (p=0.12, note: UFH + <i>planned</i> GPI rate was 10.6%) • Post PCI infusion: infusion 11.0% vs. no infusion 11.9% (p=0.34) • Major bleeding: 1.4% vs. 2.5%, RR 0.55 (p<0.001) • Death: 1.7% vs. 2.3%, RR 0.71 (p=0.04)
BRIGHT (2015)	Incl: STEMI or NSTEMI Excl: Prior anticoag	Three arms: 1) Bivalirudin + post PCI infusion (30 min – 4 hr) 2) UFH 3) UFH + tirofiban	<ul style="list-style-type: none"> • Net events: MACE + or any bleeding • MACE • Any bleeding 	n=2194 STEMI 90% Clopidogrel 100% Radial access 78.5%	<ul style="list-style-type: none"> • Arm 1 vs. 2: 8.8% vs. 13.2%, RR 0.67 (p=0.008) • Arm 1 vs. 3: 8.8% vs. 17.0%, RR 0.52 (p<0.001) • No differences in MACE • Bleeding: 4.1% vs. 7.5% vs. 12.3% (p<0.001)

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

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

Bivalirudin and UFH are two of the most extensively studied adjunctive anticoagulants for primary PCI. The HORIZONS-AMI study with bivalirudin established efficacy and safety in PCI therapy in patients with STEMI, which showed bivalirudin to be noninferior to UFH with respect to ischemic outcomes (despite an increase in acute stent thrombosis) while reducing major bleeding outcomes (Stone 2008). Because HORIZONS-AMI is almost a decade old, clinicians have questioned whether its results are still valid. Percutaneous coronary intervention treatments have rapidly evolved over the past 15 years, potentially affecting the study’s applicability to current practices. Some important variables to consider when comparing studies include the types of stents used, radial versus femoral access, use of GPIs, and use, choice, and dosage of P2Y₁₂ inhibitors. Some recent studies using contemporary PCI practices

have provided similar results to HORIZONS-AMI (see Table 1-3) (Kastrati 2011; Valgimigli 2015a; Steg 2013; Han 2015).

In contrast, other recent studies have challenged the superiority of bivalirudin over UFH, causing much debate. The HEAT-PPCI (n=1812) trial compared bivalirudin with UFH with provisional GPI use for either arm in patients with STEMI undergoing primary PCI (Shahzad 2014). Most patients received ticagrelor (62%) or prasugrel (28%), and 81% had a radial artery approach. The groups had similar GPI use (13% vs. 15%). The outcomes differed from previous studies in that ischemic events were more common with bivalirudin (8.7% vs. 5.7%, RR 1.54, p=0.01), and the incidence of major bleeding did not differ between the two groups, possibly because of the more stringent bleeding definition used in the trial. Although previous studies with bivalirudin in subsets of troponin-positive patients have trended toward worse outcomes compared with heparin plus GPI (Stone 2006; Kastrati 2011), this study defied the prevalent view that bivalirudin is superior in PCI. Possible reasons for the discordant results include low use of GPIs (possibly because of the high use of newer P2Y₁₂ inhibitors) and more access by the radial artery.

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

compared bivalirudin plus prasugrel with UFH plus clopidogrel in patients with STEMI undergoing PCI. The study was terminated early because of slow recruitment (n=548 of planned 1240). All patients underwent femoral arterial access, and GPII use was low (3% vs. 6%). The study was unable to show differences in ischemic or bleeding outcomes, although it was underpowered. These newer data challenge the idea that bivalirudin improves patient outcomes. However, newer practices such as use of radial access and decreased GPII, as well as newer P2Y₁₂ inhibitor use may lead to outcomes with UFH to be more similar to those of bivalirudin and provide an overall more attractive and cost-effective treatment.

Other options for anticoagulation in the PCI setting include enoxaparin and fondaparinux. Enoxaparin dosing is different for patients with STEMI, who are generally taken emergently to

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

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

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

Agent	Mechanism of Action	Utility	Dosing	Dose Adjustments	Monitoring	Onset	Elimination Pathway	Recovery of Platelet Function
Aspirin	Inhibits Thromboxane A ₂ production	Treatment of ACS (all phases) and secondary prevention; prevention of stent thrombosis	162–325 mg (acute); 81–325 mg (chronic)	None	Bleeding, gastric adverse effects, allergic reactions	~1–2 hr; 20 min if chewed	Hepatic conjugation; renal excretion Platelet turnover – irreversibly binds to platelets	~5 days
Clopidogrel	Thienopyridine P2Y ₁₂ inhibitor – requires 2-step metabolism to active metabolite	Treatment of ACS (all phases) and secondary prevention; prevention of stent thrombosis	300–600 mg (acute); 75 mg daily (chronic)	None	Bleeding	~2 hr (600 mg) ~6 hr (300 mg) ~3–5 days (75 mg daily)	Platelet turnover – irreversibly binds to platelets	~5–7 days
Prasugrel	Thienopyridine P2Y ₁₂ inhibitor – requires 1-step metabolism to active metabolite	Treatment of ACS associated with PCI, prevention of stent thrombosis	60 mg (acute); 10 mg daily (chronic)	Reduce to 5 mg daily if weight < 60 kg	Bleeding	~30 min	Platelet turnover – irreversibly binds to platelets	~5–10 days
Ticagrelor	P2Y ₁₂ inhibitor	Treatment of ACS with or without PCI; prevention of stent thrombosis	180 mg (acute); 90 mg BID (chronic)	Avoid use in severe hepatic impairment	Bleeding, dyspnea, uric acid concentrations	~30 min	Hepatic by CYP3A4 (contraindicated with strong inhibitors/inducers); inhibits P-glycoprotein	~3–5 days

(Continued)

Table 1-5. (Continued)

Agent	Mechanism of Action	Utility	Dosing	Dose Adjustments	Monitoring	Onset	Elimination Pathway	Recovery of Platelet Function
Cangrelor	P2Y ₁₂ inhibitor	Procedural antiplatelet therapy for PCI	PCI: 30 mcg/kg IV bolus, 4 mcg/kg/min infusion for at least 2 hr Bridge to surgery: 0.75 mcg/kg/min	None	Bleeding	2 min (bolus)	Plasma dephosphorylation	~1 hr
Eptifibatid	GPI	Procedural antiplatelet therapy for PCI	180 mcg/kg IV bolus (max 22.6 mg) x 2 for PCI, followed by 2 mcg/kg/min (max 15 mg/hr) infusion for 18-24 hr (operator discretion)	Reduce infusion to 1 mcg/kg/min if CrCl < 50 mL/min; contraindicated in ESRD	Bleeding, Plt	Immediate (bolus)	Primarily renal	~4-8 hr
Tirofiban	GPI	Procedural antiplatelet therapy for PCI	25 mcg/kg IV bolus followed by 0.15 mcg/kg/min for 18-24 hr (operator discretion)	Reduce to 0.075 mcg/kg/min if CrCl < 60 mL/min	Bleeding, Plt	Immediate (bolus)	Primary renal	~4-8 hr
Abciximab	GPI	Procedural antiplatelet therapy for PCI	0.25 mg/kg IV/IC bolus, followed by 0.125 mcg/kg/min (max 10 mcg/min) for 12 hr	None	Bleeding, Plt	Immediate (bolus)	Proteolytic cleavage	12-24 hr

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

include an intravenous bolus at the time of PCI and a post-procedural course to prevent acute stent thrombosis and allow for oral P2Y₁₂ inhibitor onset. Recently, the advent of high-dose bivalirudin and more rapidly acting oral P2Y₁₂ inhibitors has largely supplanted the routine use of procedural GPI through improved safety indices. Today, much GPI use is therefore through so-called “bailout” (i.e., non-planned use), though this approach has not been prospectively evaluated. These uses are largely procedural phenomena such as slow-reflow of an occluded coronary artery (implying distal or microvascular occlusion), high-risk interventions, or large clot burden at the operator’s discretion.

Continuous intravenous cangrelor during PCI offers an attractive alternative to pre-procedural (or later) P2Y₁₂ inhibitor preloading as a reversible and short-acting P2Y₁₂ inhibitor. In the CHAMPION-PHOENIX trial, intravenous cangrelor reduced

a composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours compared with clopidogrel (4.7% vs. 5.9%, p=0.005), the benefit for which persisted up to 30 days post-procedure (Table 1-6) (Bhatt 2013). Cangrelor also reduced procedural thrombotic events, including stent thrombosis, compared with clopidogrel when both therapies were given at the time of PCI. Various bleeding indices were also increased with cangrelor relative to clopidogrel, some of which were statistically different. Of importance, intravenous cangrelor must be carefully transitioned to an oral P2Y₁₂ inhibitor. There is a competitive pharmacodynamic interaction such that thienopyridine P2Y₁₂ inhibitors must be given after cangrelor is discontinued and no sooner because the active metabolite generated by these compounds is unstable and may be metabolized before the offset of cangrelor (Steinhuibl 2008). Ticagrelor may be used irrespective of

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

Study (Year)	Pertinent Inclusion/Exclusion Criteria	Intervention/Methods	End Points	Pertinent Baseline Characteristics	Outcomes
CURE (2001)	Incl: NSTEMI ACS Excl: STEMI	1. Aspirin + Clopidogrel 300 mg loading dose followed by 75 mg daily for 3–12 mo 2. Aspirin + Placebo	<ul style="list-style-type: none"> • Composite: death, nonfatal MI, stroke • Bleeding (as defined by trial) 	n=12,562 ~67% with ECG changes Only ~36% receiving revascularization (PCI + CABG) and ~20% receiving PCI	<ul style="list-style-type: none"> • Composite: Clopidogrel 9.3% vs. 11.4% (p<0.001) • Major Bleeding (trial-defined): Clopidogrel 3.7% vs. 2.7% (p=0.001)
CLARITY (2005)	Incl: STEMI receiving fibrinolytics Excl: High risk of bleeding, including age > 75	1. Clopidogrel 300 mg followed by 75 mg daily until at least hospital discharge or day 8 2. Placebo	<ul style="list-style-type: none"> • Composite: occluded infarct-related artery, death, recurrent MI • TIMI major bleeding 	n=3491 ~47% receiving tenecteplase ~30% receiving LMWH ~93% received coronary angiography	<ul style="list-style-type: none"> • Composite: Clopidogrel 15.0% vs. 21.7% (p<0.001) • TIMI major bleeding (30 days): Clopidogrel 1.9% vs. 1.7% (p=0.80)
ISAR-REACT 2 (2006)	Incl: NSTEMI ACS Excl: STEMI, hemodynamic instability, pericarditis, high risk of bleeding incl oral anticoagulation	1. Clopidogrel 600 mg (at least 2 hr before PCI) + placebo and intra-procedural heparin 2. Clopidogrel 600 mg (at least 2 hr before PCI) + abciximab and intra-procedural heparin	<ul style="list-style-type: none"> • Composite: death, MI, urgent target vessel revascularization (30 day) • TIMI major bleeding (30 day) 	n=2022 ~25% with prior MI ~50% troponin-positive ~50% receiving DES	<ul style="list-style-type: none"> • Composite: Abciximab 8.9% vs. 11.9% (p=0.03) • Composite (troponin-negative): Abciximab 4.6% vs. 4.6% (p=0.98) • TIMI major bleeding: Abciximab 1.4% vs. 1.4% (p=NS)
TRITON (2007)	Incl: All patients with ACS intended for PCI Excl: Bleeding history	1. Prasugrel 60 mg followed by 10 mg daily x 15 mo 2. Clopidogrel 300 mg followed by 75 mg daily x 15 mo	<ul style="list-style-type: none"> • Composite: death, MI, stroke • TIMI major bleeding (non-CABG related) 	n=13,608 26% STEMI 23% with diabetes 99% of patients received PCI ~47% with DES placement	<ul style="list-style-type: none"> • Composite: Prasugrel 9.9% vs. 12.1% (p<0.001) • TIMI major bleeding (non-CABG): Prasugrel 2.4% vs. 1.8% (p=0.03)
PLATO (2009)	Incl: All patients with ACS Excl: Concomitant strong CYP3A4 inhibitor/inducer, fibrinolysis	1. Ticagrelor 180 mg followed by 90 mg BID x 12 mo 2. Clopidogrel 300–600 mg followed by 75 mg daily x 12 mo	<ul style="list-style-type: none"> • Composite: death, MI, stroke • Major bleeding (as defined by trial) 	n=18,624 ~60% receiving PCI ~18% receiving DES ~4% receiving CABG	<ul style="list-style-type: none"> • Composite: Ticagrelor 9.8% vs. 11.7% (p<0.001) • Mortality: Ticagrelor 4.5% vs. 5.9% (p<0.001) • Non-CABG TIMI major bleeding: Ticagrelor 2.8% vs. 2.2%, p=0.03
CHAMPION-PHOENIX (2013)	Incl: PCI, both elective and all ACS Excl: Fibrinolytics	1. Cangrelor 30 mcg/kg followed by 4 mcg/kg/min for 2 hr 2. Clopidogrel 300–600 mg	<ul style="list-style-type: none"> • Composite: death, MI, ischemia-driven revascularization, stent thrombosis at 48 hr • GUSTO severe bleeding at 48 hr 	n=11,145 ~57% elective PCI ~17% STEMI ~74% received 600 mg clopidogrel ~55% received DES	<ul style="list-style-type: none"> • Composite: Cangrelor 4.7% vs. 5.9% (p=0.005) • Stent thrombosis: Cangrelor 0.8% vs. 1.4% (p=0.01) • GUSTO severe bleeding: Cangrelor 0.2% vs. 0.1% (p=0.44) • Any blood transfusion: Cangrelor 0.5% vs. 0.3% (p=0.16) • ACUITY major bleeding: Cangrelor 5.2% vs. 3.1% (p<0.0001) (femoral); 1.5% vs. 0.7% (p=0.04) (radial)

LMWH = low-molecular-weight heparin.

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

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

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

Early Invasive Strategy

Pre-procedure

Antithrombotic therapies in patients with NSTEMI ACS parallel therapies in patients with STEMI in many ways. Stable patients with NSTEMI ACS undergoing an early invasive strategy typically do not receive an emergency PCI, in contrast to patients with STEMI. This creates a defined pre-procedural period in which the patient receives various antithrombotic therapies before undergoing PCI. As with STEMI, aspirin therapy (81–325 mg) is the recommended initial treatment before cardiac catheterization (Amsterdam 2014). The P2Y₁₂ inhibitors are also recommended, though using pre-procedural P2Y₁₂ inhibition to more completely inhibit platelet-driven thrombosis remains controversial, despite the extended pre-procedural window. The superiority of earlier P2Y₁₂ inhibition has not been thoroughly demonstrated to be of value in clinical trials of patients with NSTEMI ACS (Montalescot 2014; Steinhubl 2002). Recovery of platelet function is also a more significant issue in NSTEMI ACS, regardless of drug choice, because the presence of multivessel disease in patients with NSTEMI ACS may exceed 70% of cases, though fewer than 20% will actually undergo CABG (Parikh 2010; Gogo 2007). Regardless of the timing of P2Y₁₂ inhibitor administration, the guidelines state that it is reasonable to consider ticagrelor or prasugrel over clopidogrel in patients with NSTEMI ACS, given their improved ischemic outcomes (Amsterdam 2014; Wallentin 2009; Wiviott 2007). Use of intravenous antiplatelet agents such as “upstream” GPIs (i.e., pre-procedural GPI use outside the cardiac catheterization laboratory) for NSTEMI ACS should be limited, given evidence for no additional benefit with increased bleed risk (Giugliano 2009). No data currently exist with cangrelor in the pre-procedural setting of NSTEMI ACS.

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

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

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

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

Intra-procedure

Peri-procedural management of antithrombotic therapies in NSTEMI ACS is very similar to management of STEMI. All patients should have received aspirin and possibly a P2Y₁₂ inhibitor if preloaded before PCI. If the patient was not given a P2Y₁₂ inhibitor, one should be given unless angiography identifies the need for CABG surgery. As with STEMI, GPIs are

typically only used in a bailout setting because the perceived need for aggressive intra-procedural antiplatelet therapy may be diminished by P2Y₁₂ inhibitor preloading. However, the ISAR-REACT 2 trial, in which patients with NSTEMI ACS undergoing PCI with clopidogrel preloading received either abciximab or placebo, showed superiority in reducing adverse cardiovascular outcomes with the planned use of GPIs (see Table 1-6).

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

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

CABG Surgery

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

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

Antithrombotic therapy from the onset of ACS to surgery, if necessary, involves balancing ischemic risks from further myocardial necrosis and complications of MI compared to bleeding risk during surgery. Additionally, some time-allowance for testing to ensure appropriate risk stratification for surgical candidacy is often necessary. In general, parenteral anticoagulants are continued up until the time of surgery with a period of offset immediately before surgery to allow for safe incision. This strategy is not necessarily evidence based but is commonly applied, despite no proven benefit to the patient and possible risk. Antiplatelet bridging is more complex, though recent drug approvals provide further options. However, few data exist describing the risk of thrombosis in an unrevascularized patient awaiting CABG, and no data regarding the patient populations to target. Many surgeons consider operating under the exposure of oral P2Y₁₂ inhibitors to be contraindicated and appropriate offset commensurate with their pharmacodynamic effect is warranted (5–7 days). However, platelet function recovery can be variable. Some data exist with timing surgery respective to normalized platelet function may serve to shorten the time to operation with minimal risk of bleeding compared with the label recommendations (Mahla 2012). Another option would be the use of continuous intravenous cangrelor. This therapy was investigated in the BRIDGE trial, in which patients receiving at least 72 hours of thienopyridine therapy and requiring non-emergency CABG surgery received 0.75 mcg/kg/minute or placebo until the time of surgery (Angiolillo 2012). Patients in the study (n=210) had no greater bleeding events than did patients receiving placebo. Reversible GPIs (i.e., eptifibatid) have also been used as bridging agents, though they may be associated with a greater risk of bleeding with more prolonged use.

Post-PCI Antithrombotic Therapy

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

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

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

Other studies examine short-term interruptions or premature discontinuation, like those that critically ill patients may have because of surgery or other factors. The SENS trial showed that of 194 patients post-DES who required discontinuation of DAPT for procedures, only 4 (2.2%) had significant cardiovascular events (Kim 2009). Similarly, in the DATE registry, 823 patients (not including higher-risk PCI procedures) discontinued P2Y₁₂ inhibitor therapy after 3 months (Hahn 2010). Cardiovascular outcomes and stent thrombosis events were less than 0.5% at 12 months. Although intriguing, further data are needed regarding whether a short-term interruption or premature discontinuation in a low-risk patient is safe before any definitive recommendation can be made. The risks to the patient (cardiovascular outcomes/events vs. bleeding)

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

Ischemia-Guided Strategy

Antiplatelet therapies benefiting patient populations in an ischemia-guided strategy are not significantly different from those in other ACS settings that receive revascularization. These patients still benefit from DAPT for up to 1 year post-event. The usefulness of more potent P2Y₁₂ inhibitors in addition to aspirin in patients with ACS who do not receive PCI is inconsistent. This was shown in the TRILOGY-ACS trial, in which prasugrel failed to improve ischemic outcomes compared with clopidogrel in this patient population (Roe 2012). However, ticagrelor had benefit over clopidogrel in PLATO, regardless of management strategy, and is preferred to clopidogrel in the guidelines for an ischemia-guided strategy (Amsterdam 2014; Wallentin 2009).

Parenteral anticoagulant agents also provide value in an ischemia-guided strategy. Options include intravenous UFH at a 60 units/kg bolus with an initial infusion of 12 units/kg/hour titrated to a therapeutic aPTT or anti-Xa, enoxaparin 1 mg/kg subcutaneously every 12 hours, and fondaparinux 2.5 mg subcutaneously daily. Unfractionated heparin is recommended to be continued for 48 hours, whereas enoxaparin and fondaparinux are recommended to be continued for the duration of the hospital stay. If, however, the decision is later made to undergo PCI, these agents should be discontinued afterward. Guidelines do not give any preference to one agent over another (Amsterdam 2014). Enoxaparin has been compared with UFH in various studies, showing a significant reduction in ischemic outcomes (Antman 1999; Cohen 1997; Blazing 2004). However, most of these studies were conducted before modern-era P2Y₁₂ inhibitors, which limits them. Fondaparinux was studied in the previously mentioned OASIS-5 trial, which included both patients who underwent an early invasive strategy and those who underwent an ischemia-guided strategy. Fondaparinux was noninferior to enoxaparin with a decreased incidence of bleeding, though this may be related to the lower-intensity dosing strategy in the fondaparinux arm.

MANAGEMENT OF CHRONIC ANTITHROMBOTIC PHARMACOTHERAPY

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

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

The principal factors that aid the clinician in assessing the risk of coronary thrombosis are whether a stent or several stents were placed in a coronary artery, the type of stent (BMS vs. DES), and the duration from the index event, with earlier times conferring higher risk. Lesser, but potentially important factors include the specific location of the stent in an artery, the myocardial territory affected, procedural factors such as the use of overlapping stents, bifurcation lesions, and the length of stent chosen. Ideally, all antithrombotic therapy prescribed for either secondary prevention or prevention of coronary stent thrombosis should be continued in a critically ill patient in the absence of contraindications. The consequences of stent thrombosis tend to be quite severe, resulting in death or MI in over 60% of patients (Cutlip 2001). However, when faced with higher bleeding risk scenarios or critical illness related to bleeding events, several additional scenarios may be considered. In the absence of coronary stents, DAPT used for secondary prevention likely can be temporarily held or at least minimized to aspirin only to provide a balance of protection versus bleeding risk. In a patient with coronary stents, P2Y₁₂ inhibitors can generally be temporarily held after 1 month after BMS placement and 12 months after DES placement. Because very late stent thrombosis still occurs with DES, some patients may be recommended for lifetime DAPT. It is therefore recommended to engage cardiologists in this discussion, if possible, even if stent placement occurred more than 12 months earlier. In a patient with a high risk of bleeding or an active bleeding event, guidelines generally suggest discontinuing DAPT after 2 weeks of therapy post-BMS and 6 months of DES therapy may be safe, though again, these decisions should be made in concert with cardiology consultation (Levine 2016). A patient for whom DAPT must be discontinued secondary to life-threatening bleeding should receive consultation with cardiology to determine the best course of action. Use of aspirin-only regimens in these scenarios may provide the best balance of bleeding versus protection. In the STARS trial, electively placed, older-generation coronary stents protected with aspirin only (325 mg/day) produced a 30-day event rate of adverse cardiovascular effects of 3.6% (Leon 1998). Although inferior to a regimen containing DAPT, this may provide an acceptable approximation of risk if faced with a catastrophic bleeding scenario.

MANAGEMENT OF ADVERSE EFFECTS FROM ANTITHROMBOTIC PHARMACOTHERAPY

Bleeding

Although coronary thrombosis can be catastrophic, the negative effects of bleeding associated with antithrombotic therapy should not be underestimated. Although previously seen as simply an undesired adverse effect, bleeding has been shown to be associated with increased morbidity and mortality, and is now regarded as an important clinical outcome (Steg 2011). Some possible explanations for this include prolonged cessation of antiplatelet therapy, endogenous prothrombotic rebound, and increased sympathetic response resulting in myocardial ischemia. Risk factors for bleeding include older age, female sex, lower body weight, invasive procedures, renal insufficiency, and history of bleeding. Newer oral P2Y₁₂ agents, GPI, triple therapy with DAPT and an anticoagulant, and antithrombotic agents not adjusted for renal dysfunction all increase the risk of bleeding.

Strategies to reduce the risk of bleeding should include carefully selected patients for invasive procedures, consideration for delaying procedures in patients with lower ischemic risk and high bleed risk (e.g., non-urgent CABG surgery for patient who just received a P2Y₁₂ inhibitor). Procedural techniques can reduce bleeding risk, such as radial artery approaches to PCI versus femoral approaches. As mentioned previously, the radial artery approach to PCI access site decreases the incidence of bleeding and is quickly becoming more prevalent in select centers. This selection of access site may also influence post-PCI decisions as they relate to the risk of bleeding. For example, the risk of continuing anticoagulation post-PCI may be higher in someone who underwent a femoral artery approach versus a radial artery approach.

Antithrombotic medications clearly affect bleeding risk, and many considerations need to be made to minimize that risk. Appropriate selection, dosing, and duration of antithrombotic medications are fundamental to reducing bleeding risks. The P2Y₁₂ inhibitors may have varying efficacy and safety in different populations, such as the increased risk of bleeding of prasugrel over clopidogrel without improved efficacy in patients with NSTEMI ACS treated with an ischemia-guided strategy (Roe 2012). Thus, proper selection of agents can help minimize unnecessary risk of excess bleeding. For patients with a high risk of bleeding undergoing PCI, either the use of bivalirudin or the avoidance of GPI may be warranted. Triple antithrombotic therapy with aspirin, a P2Y₁₂ inhibitor, and an anticoagulant significantly increases the risk of bleeding and should be avoided, when possible. Many antithrombotic medications need dose adjustments or drug avoidance based on renal function (see Table 1-3) or other variables such as age and weight (prasugrel, apixaban). All current guidelines prefer aspirin 81 mg to higher doses as this has been shown to have equal efficacy with reduced GI bleeding

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

Other Severe Adverse Effects

Thrombocytopenia

Registries of patients with ACS have shown the incidence of thrombocytopenia as 1.6%–13%, depending on the definition

of thrombocytopenia (Gore 2009; Wang 2009). They have also shown increased mortality in patients who develop thrombocytopenia, as well increased bleeding and reinfarction. Thus, monitoring platelets in these patients is critical/necessary. Various antithrombotic medications can lead to thrombocytopenia.

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

Patient Care Scenario

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

ANSWER:

Although interrupting DAPT is highly discouraged within the first 6–12 months of DES placement, it must be considered in severe circumstances. An ICH is a devastating major bleed because it cannot be compressed and can cause rapid, permanent damage if not controlled. There are few data to guide clinicians in these situations, and management is based largely on expert opinion (ideally with both an interventional cardiologist and a neurosurgeon). In less severe non-ICH bleeds and when duration of DAPT is complete or near-complete, continuing aspirin only and discontinuing the P2Y₁₂ agent can be considered. The decision is more challenging in more severe

consult is placed. Which one of the following is the most appropriate urgent management of M.A.'s stent anti-thrombotic therapy?

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

bleeds, or if stents were recently placed, and should be made on a patient-specific basis. When the ICH has led to seizures and intubation, discontinuing both agents is necessary. Discontinuing DAPT will likely increase the risk of stent thrombosis. However, continuing antithrombotic therapy poses a definite, real risk of an exacerbating the life-threatening bleed. In conjunction with a neurosurgery or neurology consultation, if it appears clinically and radiologically that the ICH has stabilized, reinitiating aspirin and sequentially (if indicated) the P2Y₁₂ inhibitor can then be considered.

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2. Okada T, Nakase T, Sasaki M, et al. Do the antithrombotic therapy at the time of intracerebral hemorrhage influence clinical outcome? Analysis between the difference of antiplatelet and anticoagulant agents and clinical course. *J Stroke Cerebrovasc Dis* 2014;23:1781-8.

Heparin-induced thrombocytopenia is another rare form of thrombocytopenia that may occur in any patient exposed to heparin products. Endogenous platelet factor 4 (PF4) binds to heparin in the plasma. Heparin-induced thrombocytopenia can occur when these PF4-heparin complexes form antibodies that then bind to platelets, causing platelet activation, aggregation, clot formation, and consumptive thrombocytopenia. Acute coronary syndrome registries have reported a 0.3% incidence in patients with ACS (Gore 2009). The incidence is likely higher in cardiac surgery patients because of large amounts of intraoperative heparin exposure and PF4 release ranging from 1%–3% (Matthai 2010). Heparin-induced thrombocytopenia is characterized by a decline in platelets to less than 150,000/mm³ or a 50% decrease from baseline, occurring 5–14 days after heparin exposure. Unlike GPI-associated thrombocytopenia in which the platelet nadir is typically 20,000/mm³, HIT platelet nadirs are typically closer to 50,000/mm³. This platelet reduction can also occur within 1 day if patients have had exposure within the past 100 days. Although these timelines may overlap with thrombocytopenia occurring with thienopyridines, severe bleeding associated with GPI-associated thrombocytopenia usually does not occur in HIT and can help distinguish the diagnosis as well as the timing and nadir of the platelet decrease. Although laboratory testing may help diagnose HIT, it is ultimately a clinical diagnosis. If suspicion is high, all heparin products must be discontinued (including low-molecular-weight heparin, heparin flushes, and heparinized catheters), and a direct thrombin inhibitor should be initiated to prevent thromboses. A complete discussion of the evaluation and treatment of HIT is beyond the scope of this chapter, but bivalirudin use is preferred with a history of HIT or if HIT is suspected and anticoagulation is indicated because of the clinical trial data associated with bivalirudin in patients with ACS.

Other Adverse Effects

Ticagrelor and cangrelor cause some unique adverse drug reactions, such as dyspnea and bradycardia, as a result of their structural relationship with adenosine. Dyspnea is a common symptom of many disease states and can potentially be a warning sign for disease exacerbation. In the cardiac patient, dyspnea of heart failure may be a presenting sign of worsening ischemia or progressive heart failure. Clinicians must be prudent in assessing the cause of dyspnea, as it may allow for an opportunity to intervene before a patient decompensates. Unfortunately, dyspnea has a very broad differential diagnosis with many triggers, including non-disease-related triggers. The mechanism of P2Y₁₂ inhibitor-induced dyspnea is controversial. Some argue that ticagrelor prevents adenosine reuptake and promotes adenosine-induced dyspnea, though this theory has been debated (van den Berg 2015). The incidence and consequence of dyspnea related to ticagrelor and cangrelor is not well defined. Since it was identified, many studies have described an increased risk of dyspnea

with both agents (Cattaneo 2012; Wallentin 2009; Bhatt 2013). These studies have shown that dyspnea with ticagrelor may occur within 24 hours to 7 days after initiation, and in the clinical trials, it occurred in about 15%–38% of patients (Sanchez-Galian 2015; Cattaneo 2012). Although the dyspnea is typically mild to moderate, it can be severe enough to require drug discontinuation in up to 4% of patients. If needed, discontinuation of ticagrelor typically occurs in the first 1–2 weeks (Bonaca 2015). There are no well-defined recommendations for ticagrelor-induced dyspnea, though most cases do not require drug discontinuation. All other causes of dyspnea must first be ruled out. It may be challenging to distinguish dyspnea of cardiac etiology versus drug-induced dyspnea in a patient with a recent MI. If dyspnea is thought to be the result of a specific disease process, the presence or absence of other clinical features may help narrow the etiology. Currently, no treatments exist for ticagrelor-induced dyspnea. If identified, ticagrelor may need to be discontinued and replaced with another P2Y₁₂ inhibitor.

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

CONCLUSION

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

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

Practice Points

In determining the optimal antithrombotic therapy for a critically ill patient with ACS, practitioners should consider the following:

- Try to classify the potential infarct according to the universal definition. If thought to be a type 2 infarct (supply/demand imbalance), consider withholding antithrombotic therapy, particularly if there is a potential for harm.
- Choice and type of antithrombotic therapy depend on the revascularization modality (if any) and patient-specific factors.
- Chronic antithrombotic therapy prescribed for ACS may be withheld in certain scenarios in critically ill patients, but consider involving a cardiologist in this determination, especially if the patient has a history of coronary stents.
- Antithrombotic therapy is associated with various toxicities, especially bleeding. Management of bleeding and recent history of coronary stenting is complex, and treatment decisions should largely be made on a patient-specific basis.

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

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

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

1. According to the universal definition of MI, which one of the following types of infarction is most consistent with M.J.'s presentation?
 - A. 1
 - B. 2
 - C. 3
 - D. 4
2. M.J. is given a medical diagnosis of, and meets the criteria for, a non-ST-segment elevation myocardial infarction (NSTEMI). Which one of the following would be the most appropriate anticoagulation therapy to promote clot stabilization until reperfusion and/or further testing modalities can be initiated for M.J.?
 - A. Give unfractionated heparin (UFH).
 - B. Give enoxaparin.
 - C. Give fondaparinux.
 - D. Anticoagulation therapy is not necessary.
3. Which one of the following best describes the optimal management of M.J.'s chronic dual antiplatelet therapy (DAPT) in the acute setting?
 - A. Discontinue clopidogrel and continue aspirin.
 - B. Discontinue aspirin and clopidogrel.
 - C. More information is needed about the patient's stent.
 - D. Continue both aspirin and clopidogrel.

Questions 4–6 pertain to the following case.

J.M., a 65-year-old man with a history of tobacco abuse, hypertension, type 2 diabetes, peripheral arterial disease, and seizure disorder secondary to traumatic brain injury, presents to the ED with persistent chest pain. In the ED, his chest pain is fairly refractory to continuous nitroglycerin, and he is

transferred to the CCU for closer monitoring. J.M.'s ECG is consistent with diffuse ST depression and slight ST-elevation (non-STEMI criteria) in aVR, suggestive of disease in the left main coronary artery. Troponin is elevated at 1.5 ng/mL. His home drugs include aspirin 81 mg daily, metformin 1000 mg twice daily, metoprolol 50 mg twice daily, and phenytoin 300 mg at bedtime. J.M. received enoxaparin 1 mg/kg subcutaneously x 1 dose in the ED. His vital signs include blood pressure 100/60 mm Hg and heart rate 72 beats/minute.

4. According to the universal definition of MI, which one of the following types of infarction is most consistent with J.M.'s presentation?
 - A. 1
 - B. 2
 - C. 3
 - D. 4
5. The team is concerned that J.M. may have left main coronary disease, given his ECG findings, and therefore may require urgent cardiac surgery if identified through coronary angiography. Given this concern, which one of the following antiplatelet regimens is most appropriate while J.M. awaits cardiac catheterization (expected within 1 hour)?
 - A. Continue his aspirin therapy only.
 - B. Administer 60 mg of prasugrel, followed by 10 mg daily.
 - C. Administer 180 mg of ticagrelor, followed by 90 mg twice daily.
 - D. Initiate cangrelor at 0.75 mcg/kg/minute continuous intravenous infusion.
6. Which one of the following is the most appropriate action regarding J.M.'s anticoagulation therapy?
 - A. Discontinue all anticoagulation, given his potential for upcoming cardiac surgery.
 - B. Administer UFH (60-unit/kg bolus, followed by 12 units/kg/hour infusion) immediately on arrival at the critical care ICU.
 - C. Continue therapeutic enoxaparin with the next dose 12 hours from his first dose in the ED.
 - D. Change to fondaparinux 2.5 mg subcutaneously daily (first dose the following day) to reduce his risk of bleeding.
7. A 59-year-old woman presents for an emergency appendectomy after complaints of abrupt-onset abdominal pain. She has a history of coronary artery disease, including stenting of her left circumflex artery 8 months ago with drug-eluting stent (DES) placement (specific stent unknown). In addition, she has a medical history

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

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

Questions 8–10 pertain to the following case.

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

- 8. Which one of the following is the best option to initiate for K.L.'s anticoagulation therapy?
 - A. Fondaparinux
 - B. Bivalirudin
 - C. Enoxaparin
 - D. UFH
- 9. K.L. has coronary disease in three discrete arteries, best treated with coronary artery bypass grafting (CABG) surgery. He undergoes a workup regarding his candidacy for surgery. A few days later, he develops thrombocytopenia with a greater than 50% drop in platelet count from a baseline of 300,000/mm³ to 128,000/mm³. The team sends laboratory monitoring, including platelet factor 4 and serotonin release assay, which will have a minimum of 48 hours' turnaround. Which one of the following is the most appropriate action regarding K.L.'s anticoagulation?
 - A. Discontinue heparin, begin enoxaparin at 1 mg/kg subcutaneously every 12 hours.

- B. Continue heparin and initiate cangrelor at 0.75 mcg/kg/minute.
 - C. Discontinue heparin and initiate eptifibatid at 2 mcg/kg/minute.
 - D. Discontinue heparin and initiate therapeutic bivalirudin, titrated to therapeutic aPTT.
- 10. K.L.'s dynamic chest pain continues after the procedure. The team is trying to expedite his surgery. In the interim, they wish to initiate some antiplatelet therapy as a bridge to surgery. Which one of the following is best to recommend for K.L.?
 - A. Initiate eptifibatid at 2 mcg/kg/minute.
 - B. Load with 180 mg of ticagrelor x 1.
 - C. Load with 60 mg of prasugrel x 1.
 - D. Initiate cangrelor at 0.75 mcg/kg/minute.
 - 11. Your hospital receives a call for potential transfer from a rural hospital. A 68-year-old man presented to the ED with complaints of nausea, vomiting, and diaphoresis. His medical history includes hypertension (reportedly well controlled with current blood pressure 135/75 mm Hg and heart rate 90 beats/minute) and dyslipidemia. Fifteen minutes after being seen by paramedics, his ECG showed ST elevations in leads V2–V5. He was immediately given aspirin, enoxaparin, and nitroglycerin. The ED physician at the outside hospital consults with your cardiologist about potentially transferring the patient for cardiac catheterization versus giving fibrinolytic therapy. The patient has no known contraindications for fibrinolytics. The patient's estimated travel time is 55 minutes. Which one of the following is best to recommend for this patient?
 - A. Give clopidogrel 300 mg now plus tenecteplase; then have the patient transferred to your center for cardiac catheterization.
 - B. Give clopidogrel 600 mg now plus tenecteplase; then have the patient transferred to your center for cardiac catheterization.
 - C. Give clopidogrel 300 mg and have the patient immediately transferred to your center for cardiac catheterization.
 - D. Give clopidogrel 600 mg and have the patient immediately transferred to your center for cardiac catheterization.

Questions 12 and 13 pertain to the following case.

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

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

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

13. G.G. received 60 mg of prasugrel during PCI as well as bailout abciximab for slow flow after revascularization. Two hours after arriving at your ICU, he continues to bleed from his access site. A CBC is normal except for a platelet count of 26,000/mm³. G.G.'s baseline platelet count on admission was within normal limits. Which one of the following drugs most likely caused G.G.'s thrombocytopenia?

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

14. A 76-year-old man presents to your hospital for an inguinal hernia repair. He has a medical history of hypertension, dyslipidemia, and remote MI treated with a DES several years earlier (unknown vessel and no longer taking P2Y₁₂ inhibitor). On postoperative day 1, the patient develops chest pain. An ECG shows ST depressions in leads V1–V3. The patient is given aspirin, clopidogrel, and heparin. He then experienced pulseless ventricular tachycardia. Cardiopulmonary resuscitation is initiated, and the patient is successfully resuscitated and transferred to your ICU. He then has hematemesis and hypotension, prompting the team to hold clopidogrel. Three days later, the patient has no longer had any bleeding, and his hemoglobin and hemodynamics are stable. An EGD reveals friable mucosa but no obvious signs of bleeding. Which one of the following is best to recommend regarding this patient's P2Y₁₂ therapy in the acute setting?

- A. Hold clopidogrel therapy, given the recent GI bleed.
- B. Reinitiate clopidogrel.
- C. Change to prasugrel therapy.
- D. Initiate cangrelor therapy while awaiting a final decision on oral P2Y₁₂ therapy.

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

the incidence of moderate or severe bleeding using the GUSTO scale. Outcomes are as follows:

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

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

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

Questions 16–18 pertain to the following case.

J.W. is a 63-year-old man (weight 80 kg) with a medical history of alcohol abuse, cirrhosis, GI bleed (1 year ago), and poor adherence to medical care. He is admitted to the medical ICU with altered mental status, hyperammonemia, jaundice, and fluid overload. On day 2 of admission, he has complaints of chest pressure and is found to have ST-segment depressions in leads V₁–V₄. The decision is made to pursue an ischemia-guided strategy for treatment of non-ST-segment elevation acute coronary syndrome (NSTEMI ACS).

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

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

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

- A. A 6400-unit intravenous bolus followed by 1440 units/hour for 48 hours
 - B. A 6400-unit intravenous bolus followed by 1440 units/hour for 8 days
 - C. A 4800-unit intravenous bolus followed by 960 units/hour for 48 hours
 - D. A 4800-unit intravenous bolus followed by 960 units/hour for 8 days
18. Which one of the following would best attenuate J.W.'s risk of bleeding?
- A. Initiate pantoprazole continuous infusion at 8 mg/hour.
 - B. Initiate pantoprazole 40 mg orally daily.
 - C. Separate out administration times of antithrombotic drugs.
 - D. Give lower doses of one or more antithrombotic regimens.
19. A 55-year-old man has a medical history of STEMI (3 days ago) with an asymptomatic left ventricular ejection fraction 24 hours after the event of 40%, tobacco abuse, hypertension, and diabetes. He had two DESs placed and is awaiting hospital discharge on the acute care floor on aspirin 81 mg, ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, carvedilol 12.5 mg twice daily, and lisinopril 5 mg twice daily. During morning rounds, your team receives a page that the patient is feeling short of breath. A 12-lead ECG is unchanged from his baseline. Cardiac biomarkers are negative. His lungs are clear to auscultation, and chest radiography is clear without evidence of edema or infectious processes. His Sao_2 is 99%, and his respiratory rate is 28 breaths/minute. A bedside arterial blood gas fails to identify evidence of CO_2 retention. Which one of the following is the most likely cause of this patient's symptoms?
- A. Ischemic heart disease
 - B. Ticagrelor
 - C. Lisinopril
 - D. Acute decompensated heart failure
20. Which one of the following is most likely to result in patient harm secondary to medical error?
- A. Administration of ticagrelor on an every-12-hour versus twice-daily schedule
 - B. Coadministration of clopidogrel with a proton pump inhibitor
 - C. Administration of a loading dose of clopidogrel during a cangrelor infusion in PCI
 - D. Administration of 600 mg of clopidogrel instead of 300 mg for a loading dose

Learner Chapter Evaluation: Antithrombotic Therapies in Acute Coronary Syndrome.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish the types of myocardial infarction that can occur in critically ill patients
13. Evaluate the acute use of antiplatelet and anticoagulant therapies for patients with ischemic heart disease
14. Develop appropriate management of chronic antithrombotic pharmacotherapies for ischemic heart disease in critically ill patients
15. Demonstrate appropriate management of antithrombotic toxicities and adverse effects in patients with ischemic heart disease
16. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:



Direct Oral Anticoagulants in Special Populations

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LEARNING OBJECTIVES

1. Assess the risks and benefits of direct oral anticoagulants (DOACs) compared with traditional anticoagulants.
2. Design an appropriate DOAC regimen for patients with alterations in organ function.
3. Develop an evidence-based strategy for the management of DOACs in patients with selected comorbid conditions.
4. Design a treatment approach to manage bleeding complications associated with DOACs.

ABBREVIATIONS IN THIS CHAPTER

AF	Atrial fibrillation
aPCC	Activated prothrombin complex concentrate
BARC	Bleeding academic research consortium
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DOAC	Direct oral anticoagulant
ESRD	End-stage renal disease
GIB	GI bleed
GUSTO	Global utilization of streptokinase and Tpa for occluded arteries
MS	Mitral stenosis
OAC	Oral anticoagulant
PCC	Prothrombin complex concentrate
TIMI	Thrombolysis in myocardial infarction
VHD	Valvular heart disease
VKA	Vitamin K antagonist

[*Table of other common abbreviations.*](#)

INTRODUCTION

Direct Oral Anticoagulants vs. Traditional Antithrombotic Therapies

Although warfarin has long been the standard of care for oral anticoagulants (OACs), the emergence of direct oral anticoagulants (DOACs) has yielded several options. Table 2-1 summarizes key results of major atrial fibrillation (AF) DOAC trials. Of note, in these trials, dabigatran and apixaban demonstrated a statistically significant reduction in the primary end point of stroke and systemic embolism; by comparison, rivaroxaban and edoxaban demonstrated noninferiority but not superiority (Giugliano 2013; Granger 2011; Patel 2011; Connolly 2009). All four agents were associated with reductions in hemorrhagic stroke. However, dabigatran, rivaroxaban, and edoxaban were also associated with an increased GI bleed (GIB); apixaban was associated with a GIB rate similar to warfarin, making warfarin and apixaban preferable for patients at risk of GIB. Although dabigatran and rivaroxaban were associated with rates of overall major bleeding similar to warfarin, apixaban and edoxaban were associated with overall reductions in major bleeding. Taken together, apixaban is the only agent with both a reduction in stroke and systemic embolism and a reduction in overall major bleeding.

In the AVERROES trial, 5599 patients unsuitable for warfarin were randomized to apixaban or aspirin (Connolly 2011). An interim analysis identified a 55% reduction in stroke or systemic embolism (95% CI, 0.32–0.62; $p < 0.001$) with apixaban. As in other trials comparing warfarin and antiplatelet therapy, the rate of major bleeding with apixaban and aspirin was similar ($p = 0.57$). However, a modest increase in minor bleeding was associated with apixaban (HR 1.24; 95% CI, 1.00–1.53; $p = 0.05$). Results were consistent across subgroups,

including elderly patients, decreased renal function, CHADS₂ scores, and low- and high-dose aspirin (Connolly 2011).

Table 2-2 summarizes key trials of DOACs for venous thromboembolism (VTE) treatment. In general, DOACs were associated with similar rates of VTE events compared with traditional therapy; although dabigatran and edoxaban were associated with similar rates of major bleeding, rivaroxaban and apixaban were associated with reductions in major bleeding compared with warfarin. Although no direct comparisons of DOAC agents are available, rivaroxaban or apixaban may be preferable DOACs for VTE treatment in most patients given the favorable bleeding profiles reported.

Professional guideline recommendations regarding antithrombotic agents for AF and VTE are summarized in Table 2-3. In general, most guidelines identify all OACs as therapeutic options, but DOACs are increasingly preferred. As such, it is

critical that clinicians identify strategies for using DOACs safely in a variety of populations. Although Table 2-3 refers to general populations, subsequent sections of this chapter address DOACs in special populations.

DOSING AND MANAGEMENT CONSIDERATIONS IN PATIENTS WITH ALTERATIONS IN ORGAN FUNCTION

Renal Dysfunction

Renal dysfunction is common in critically ill patients. Direct oral anticoagulants are partially eliminated by renal clearance (Table 2-4) and require dose adjustments for varying states of renal dysfunction (Table 2-5). Dabigatran is most affected by renal clearance (80%), and both ecarin clotting time (ECT) and activated PTT (aPTT) were increased in the setting of impaired renal function and concomitant dabigatran (Stangier 2008a). Rivaroxaban and edoxaban are also significantly affected by renal clearance. In subjects with renal impairment, rivaroxaban's AUC was increased by 44%, 52%, and 64%, respectively, for mild (CrCl 50–79 mL/min), moderate (CrCl 30–49 mL/min), and severe (CrCl less than 30 mL/min) renal impairment compared with subjects with normal renal function (Kubitza 2010). Edoxaban exposure was increased by 32%, 74%, and 72% in patients with mild (CrCl 50–80 mL/min), moderate (CrCl 30–50 mL/min), and severe (CrCl less than 30 mL/min) renal impairment, respectively, compared with patients having a CrCl of 80 mL/min or less, according to manufacturer information. Dabigatran, rivaroxaban, and edoxaban should be avoided in severe renal impairment, according to manufacturer recommendations. Apixaban is dose reduced from 5 mg twice daily to 2.5 mg twice daily in nonvalvular AF (not VTE) only if a patient meets two of the three criteria (see Table 2-5). A pharmacokinetic study that included 32 patients with normal (CrCl > 80 mL/min), mild (CrCl > 50 and ≤ 80 mL/min) moderate (CrCl ≥ 30 and ≤ 50 mL/min) and, severe (CrCl < 30 mL/min) renal impairment reported an apixaban AUC increase of 44% in patients with a 24-hour CrCl of 15 mL/min compared to those with normal renal function, without affecting C_{max} between groups (Chang 2016). Apixaban dosing in patients with end-stage renal disease (ESRD) receiving hemodialysis is discussed later in this section.

Many of the DOAC trials excluded patients with renal dysfunction. Trials with rivaroxaban and dabigatran excluded patients with a CrCl less than 30 mL/min, and trials with apixaban typically excluded patients with a CrCl less than 25 mL/min or an SCr greater than 2.5 mg/dL (Sardar 2014a). About 4%–20% of the patients in key clinical trials had a CrCl of 30–50 mL/min (Del-Carpio Munoz 2016; Nielsen 2015; Geldhof 2014; Sardar 2014a).

A meta-analysis analysis of 40,693 patients with mild (CrCl 50–79 mL/min; n=28,971) and moderate (CrCl 30–49 mL/min; n=11,722) renal impairment compared conventional therapy with DOAC treatment (Sardar 2014a). Data were included

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of approved direct oral anticoagulant (DOAC) indications
- Standard DOAC dosing
- General knowledge of DOAC mechanisms of action
- General knowledge of other anticoagulation options for atrial fibrillation (AF) and venous thromboembolism (VTE) (including warfarin and enoxaparin)
- General knowledge of antithrombotic management for AF and VTE, including therapy duration

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American College of Chest Physicians. [Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report](#). Chest 2016;149:315-52.
- American Heart Association, American College of Cardiology, and Heart Rhythm Society. [Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society](#). J Am Coll Cardiol 2014;64:2246-80.
- European Society of Cardiology. [Guidelines on the diagnosis and management of acute pulmonary embolism](#). Eur Heart J 2014;35:3033-80.

Table 2-1. Summary of Key AF Trials Comparing DOACs with Warfarin^a

	RE-LY (n=18,113)	ROCKET-AF (n=14,264)	ARISTOTLE (n=18,201)	ENGAGE AF-TIMI 48 (n=21,105)
Agent	Dabigatran ^b	Rivaroxaban	Apixaban	Edoxaban ^c
Stroke or systemic embolism	0.66 (0.53–0.82)	0.88 (0.75–1.03)	0.79 (0.66–0.95)	0.87 (0.73–1.04)
Stroke, all-cause	0.64 (0.51–0.81)	0.85 (0.70–1.03)	0.79 (0.65–0.95)	0.88 (0.75–1.03)
Stroke, ischemic/unspecified	0.76 (0.60–0.98)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	1.00 (0.83–1.19)
Stroke, hemorrhagic	0.26 (0.14–0.49)	0.59 (0.37–0.93)	0.51 (0.35–0.75)	0.54 (0.38–0.77)
Death, cardiovascular	0.85 (0.72–0.99)	0.89 (0.73–1.10)	0.89 (0.76–1.04)	0.86 (0.77–0.97)
Death, all-cause	0.88 (0.77–1.00)	0.85 (0.70–1.02)	0.89 (0.80–0.998)	0.92 (0.83–1.01)
Major bleeding	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	0.80 (0.71–0.91)
GI bleeding	1.50 (1.19–1.89)	1.42 (1.22–1.66)	0.89 (0.70–1.15)	1.23 (1.02–1.50)

^aValues represented as HR (95% CI) for ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48; data represented as relative risk (95% CI) for RE-LY. All data are for superiority analyses using ITT populations.

^bDabigatran 150 mg BID vs. warfarin.

^cEdoxaban 60 mg daily vs. warfarin.

BID = twice daily; ITT = intent-to-treat.

Information from: Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51; Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91; Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92; Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin. *J Am Coll Cardiol* 2015;66:2271-81; Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.

Table 2-2. Summary of Key VTE Trials Comparing DOACs with Warfarin^a

	RE-COVER Pooled Analysis (n=5107)	EINSTEIN Pooled Analysis (n=8282)	AMPLIFY (n=5395)	HOKUSAI-VTE (n=8240)
Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Primary outcome ^b	1.09 (0.76–1.57)	0.89 (0.66–1.19)	0.84 (0.60–1.18)	0.89 (0.70–1.13)
Major bleeding	0.73 (0.48–1.11) ^c	0.54 (0.37–0.79)	0.31 (0.17–0.55)	0.84 (0.59–1.21)
Intracranial hemorrhage	n=2 dabigatran vs. 9 VKA ^d	n=5 rivaroxaban vs. 13 VKA	n=3 apixaban vs. 6 VKA	n=5 edoxaban vs. n=18 VKA
GI bleed	n=101 dabigatran vs. 68 VKA ^d	n=1 rivaroxaban vs. 3 VKA ^e	n=7 apixaban vs. 18 VKA	n=1 edoxaban vs. 2 VKA ^e

^aValues presented as HR (95% CI) unless otherwise noted.

^bDabigatran, apixaban, and edoxaban data represent rate of recurrent VTE or VTE-related death; rivaroxaban data represent recurrent VTE.

^cFrom the start of any study drug (single- and double-dummy periods).

^dAdded from both the RE-COVER and RE-COVER II trials.

^eOnly fatal events reported.

VKA = vitamin K antagonist.

Information from: Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129:764-72; Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013;11:21; Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406-15.

Table 2-3. Summary of Guideline Recommendations for Oral Antithrombotic Therapy in General Populations

Guideline (yr)	AF Guidelines			VTE Guidelines	
	AHA/ACC/ HRS (2014)	ACCP (2012)	ESC (2016)	ACCP (2016)	ESC (2014)
General recommendations ^a	VKA (IA) or DOAC (IB)	OAC (1A)	OAC (IA)	AC (1B) DOAC (2B) VKA (2C)	Parenteral AC (IC) or OAC (IB)
Agent preference	N/A	DOAC (2B)	DOAC (IA)	DOAC (2B)	N/A

^aClass of recommendation and level of evidence presented in parenthesis, according to each guideline; refers specifically to general populations; see subsequent sections for recommendations regarding special populations and other considerations.

AC = anticoagulation; ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; ESC = European Society of Cardiology; N/A = not applicable; OAC = oral anticoagulant.

Information from: January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071-104; You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation. *Chest* 2012;141:e531S-e575S; Kirchhof P, Benussi S, Kotech D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Rhythm Society Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO). *Eur Heart J* 2016;37:2893-962; Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest* 2016;149:315-52; Konstantinides SV, Torbicki A, Giancarlo A, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Endorsed by the European Respiratory Society (ERS). *Eur Heart J* 2014;35:3033-73.

from 10 key trials with dabigatran, rivaroxaban, and apixaban (Table 2-6). Randomization to DOAC therapy was associated with reductions in major bleeding or clinically relevant non-major bleeding compared with conventional therapy in patients with mild renal impairment; however, this benefit

primarily occurred in patients with AF because rates were similar in patients with acute VTE. Bleeding rates were also similar between DOAC and conventional therapy in those with moderate renal impairment in both AF and VTE populations. Rates of stroke or systemic embolism (patients with AF) were

Table 2-4. Comparison of Renal Elimination in DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half-life in healthy patients	12–17 hr ^a	5–9 hr ^b	12 hr	10–14 hr
Metabolism	Plasma and hepatic esterase, PGP	CYP, PGP	CYP, PGP	CYP, PGP
Renal clearance	80%	36%	27%	50%
Removed by hemodialysis	Yes ^c	No	Minimal ^d	No

^aHalf-life 15–18 hr in mild-moderate renal impairment (CrCl 30–80 mL/min) and 28 hr in severe renal impairment (CrCl 15–30 mL/min).

^bHalf-life 11–13 hr in elderly patients.

^cUsing a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, about 49% of total dabigatran can be cleared from plasma over 4 hr. On cessation of hemodialysis, a redistribution effect of 7%–15% occurs. The effect of dialysis on dabigatran's plasma concentration would be expected to vary according to patient-specific characteristics.

^dThe dialysis clearance of apixaban is about 18 mL/min, resulting in a 14% decrease in exposure because of hemodialysis compared with off-dialysis period.

CYP = cytochrome P450 enzymes; PGP = p-glycoprotein

Information from manufacturer's package inserts.

Table 2-5. Approved Dosing for DOACs According to Renal Function^a

	Atrial Fibrillation ^b	VTE Treatment	Postoperative VTE Prophylaxis
Dabigatran	CrCl > 30 mL/min: 150 mg BID CrCl 15–30 mL/min: 75 mg BID CrCl < 15 mL/min or dialysis: No dosing recommendations provided	After 5–10 days of initial parenteral treatment: CrCl > 30 mL/min: 150 mg twice daily CrCl < 30 mL/min or dialysis: No dosing recommendations provided	CrCl > 30 mL/min: 110 mg once daily for the first day; then 220 mg daily CrCl ≤ 30 mL/min: No dosing recommendations provided
Rivaroxaban	CrCl > 50 mL/min: 20 mg daily CrCl 15–50 mL/min: 15 mg daily CrCl < 15 mL/min: Avoid	CrCl > 30 mL/min: 15 mg BID x 21 days; then 20 mg daily CrCl < 30 mL/min: Avoid	CrCl > 30 mL/min: 10 mg daily CrCl < 30 mL/min day: Avoid
Apixaban	5 mg BID If any two of following: SCr ≥ 1.5 mg/dL, age ≥ 80 yr, weight ≤ 60 kg: 2.5 mg BID	10 mg BID x 7 days; then 5 mg BID After 6 mo of above treatment: 2.5 mg BID	2.5 mg BID
Edoxaban	CrCl > 95 mL/min: AVOID CrCl 51–95 mL/min: 60 mg daily CrCl 15–50 mL/min: 30 mg daily CrCl < 15 mL/min: AVOID	After 5–10 days of initial parenteral treatment: CrCl > 50 mL/min: 60 mg daily CrCl 15–50 mL/min: 30 mg daily CrCl < 15 mL/min: AVOID Patients ≤ 60 kg: 30 mg daily	N/A

^aRenal function based on Cockcroft-Gault equation should use actual body weight.

^bDOACs are indicated for nonvalvular AF only.

Information from manufacturers' package inserts.

lower with DOAC therapy than with conventional therapy in both the mild and moderate renal impairment groups, whereas rates of VTE or VTE-related death (patients with VTE) were

similar in both mild and moderate renal impairment. Results were similar between all DOACs studied.

Another meta-analysis of key AF trials included patients with normal renal function (CrCl greater than 80 mL/min;

Table 2-6. Efficacy and Safety Results of DOACs vs. Conventional Therapy Meta-analysis

	Mild Renal Impairment (CrCl 50–79 mL/min)			Moderate Renal Impairment (CrCl 30–49 mL/min)		
	DOAC (%)	Conventional (%)	OR (95% CI)	DOAC (%)	Conventional (%)	OR (95% CI)
Major or clinically relevant nonmajor bleeding	4.8	5.5	0.81 (0.72–0.90)	6.8	7.6	0.82 (0.59–1.14)
Stroke or systemic embolism	2.9	3.8	0.70 (0.54–0.92)	3.9	5.3	0.72 (0.57–0.92)
VTE or VTE-related death	2.2	2.3	0.95 (0.41–2.17)	3.0	3.2	0.97 (0.42–2.21)

Information from: Sardar P, Chatterjee S, Herzog E, et al. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. *Can J Cardiol* 2014;30:888-97.

n=21,118), mild impairment (CrCl 50–80 mL/min; n=26,050), and moderate impairment (CrCl less than 50 mL/min; n=10,908) (Del-Carpio Munoz 2016). Use of DOACs in patients with mild and moderate renal dysfunction was associated with a reduced risk of stroke and systemic embolization (RR 0.75; 95% CI, 0.66–0.85 and RR 0.80; 95% CI, 0.68–0.94, respectively) and reduced risk of major bleeding (RR 0.87; 95% CI, 0.79–0.95 and RR 0.80; 95% CI, 0.71–0.91, respectively) compared with warfarin. Overall, meta-analyses of DOAC use in both VTE and AF with concomitant mild-moderate renal impairment have shown DOACs to have similar or improved thrombotic clinical end points and major bleeding compared with warfarin.

A single-dose, pharmacokinetic study of eight patients with ESRD requiring hemodialysis compared with matched healthy subjects showed a 36% higher apixaban exposure in patients with ESRD; clinical outcomes were not assessed (Wang 2016). At this time, no long-term data regarding apixaban use in ESRD or hemodialysis are available. The 2014 AHA-ACC-HRS AF guidelines recommend warfarin as the anticoagulant of choice for patients with severe renal impairment (CrCl < 15 mL/min) or receiving hemodialysis. Other AF and VTE guidelines offer little direction for selection of anticoagulation in patients requiring hemodialysis. Clinicians should use caution with DOACs, including apixaban, in patients with severe renal impairment as this population warrants more research. (Deal 2014).

Hepatic Dysfunction

Chronic liver disease reduces synthesis of coagulation factors and causes both qualitative and quantitative changes in platelet function; this creates challenges in anticoagulation monitoring (Graff 2013). Understanding the role of DOAC use in hepatic impairment is important for ICU clinicians, especially given that hepatic impairment is a perceived barrier to anticoagulation (Baczek 2012).

Data for DOAC use in hepatic impairment are limited to small pharmacokinetic trials. Rivaroxaban pharmacokinetics were compared between healthy subjects (n=16) and those with mild (Child-Pugh A, n=8) and moderate (Child-Pugh B, n=8) hepatic impairment (Kubitza 2013). Rivaroxaban AUC increases of 1.15- and 2.27-fold occurred in subjects with mild and moderate hepatic impairment, respectively, compared with healthy patients. This is likely related to reduced elimination and increased C_{max} in hepatic impairment. A small study comparing apixaban in healthy subjects (n=16) with apixaban in those with mild (Child-Pugh A, n=8) and moderate (Child-Pugh B, n=8) hepatic impairment showed slightly increased AUCs of 1.03 and 1.09 for mild and moderate impairment, respectively, compared with the healthy cohort, with no difference in C_{max} (Frost 2008). In a similar trial design, edoxaban decreased AUC by 4.2% and 4.8%, decreased C_{max} by 10% and 32%, and an increased half-life by 13% and 38% in patients with mild (n=8) and moderate (n=8) hepatic impairment, respectively, compared with healthy subjects (n=16) (Mendell

2012). A small, single-dose trial comparing dabigatran pharmacokinetics in healthy volunteers (n=12) with dabigatran pharmacokinetics in patients with moderate hepatic impairment (n=12, Child-Pugh B) showed no difference in AUC and C_{max} (Stangier 2008b).

All of the DOACs can be used in mild hepatic impairment if anticoagulation is deemed safe from a bleeding perspective. In moderate hepatic impairment, dabigatran and apixaban may be considered, but rivaroxaban and edoxaban should be avoided (Table 2-7). Special caution should be used in patients with hepatorenal syndrome because agents with extensive renal elimination should be avoided. In addition, because cirrhosis may cause low albumin, the effect of protein binding of DOACs should be considered when selecting an agent. According to protein binding sensitivity criteria (Delcò 2005), dabigatran is least sensitive to the effects of protein binding (Graff 2013).

Patient Care Scenario

A 64-year-old woman (height 65 inches, weight 100kg) is currently in the cardiac ICU with an acute exacerbation of her heart failure with reduced ejection fraction (EF 10%–15%). Her medical history includes ESRD currently requiring hemodialysis twice weekly and a GIB as the result of a peptic ulcer. During this admission, she is found to have a new left ventricular thrombus. The patient is currently hemodynamically stable and receiving a heparin infusion. The medical team expects discharge in 3–5 days and is seeking your advice for continued anticoagulation management. The patient notes significant issues with medication affordability because of her lack of prescription insurance.

ANSWER

There are no large clinical trials prospectively evaluating the effectiveness of DOACs compared with warfarin in left ventricular thrombus. If choosing to use a DOAC for this indication, appropriate anticoagulant dosing would most closely be extrapolated from approved VTE dosing. Whether DOAC therapy or warfarin therapy is most appropriate for this patient depends on patient-specific factors and comorbidities. The only DOAC with approved dosing in ESRD is apixaban. Apixaban dosing in acute VTE is 10 mg twice daily for the first 7 days, followed by 5 mg twice daily thereafter. Consideration for parenteral anticoagulation therapy already received may affect the initial dosing selected. Patient-specific financial barriers may also affect agent selection. None of the DOACs are currently available as a generic product, which may therefore increase the financial burden to the patient. Although warfarin is available as a generic product, ensuring adherence to laboratory monitoring would be necessary. In this case, with significant financial concerns, warfarin therapy is the most appropriate selection.

1. Kearon C, Elie A, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315–52.
2. Deal EN, Pope H, Ross W. Apixaban use among patients with severe renal impairment. *Ann Pharmacother* 2014;48:1667.

Table 2-7. DOAC Use in Hepatic Dysfunction

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Hepatic metabolism	No	Yes CYP3A4/5, CYP2J2	Yes CYP3A4 (main), CYP1A2, 2C8, 2C9, 2C19, 2J2 (all minor)	Minimal CYP3A4 (minimal)
Recommendations for use in hepatic impairment	Moderate hepatic impairment (Child-Pugh B) showed large intersubject variability, but no evidence of a consistent change in exposure or pharmacodynamics	Avoid use in moderate and severe (Child-Pugh B and C) or with any degree of hepatic disease associated with coagulopathy	No dose reduction needed for mild impairment (Child-Pugh A) No recommendations for dosing in moderate hepatic impairment (Child-Pugh B) Not recommended in severe hepatic impairment (Child-Pugh C)	No dose reduction needed for mild impairment (Child-Pugh A) Not recommended in moderate to severe hepatic impairment (Child-Pugh B or C)
Approximate hepatobiliary elimination	20%	34% (7% unchanged)	75%	65%
Protein binding	35%	92%–95%	87%	55%

Information from manufacturers' package inserts; and Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. *Clin Pharmacokinet* 2013;52:243-54.

Considerations in the Elderly Population

With current population trends predicting an increase in patients living into their 80s, all clinicians will need to be familiar with the elderly population (Nguyen 2011). Increasing age is a risk factor for stroke related to AF and VTE, but age also places patients at a higher risk of bleeding with anticoagulant therapy (Bauersachs 2012). As such, both bleeding and thrombotic event rates are often increased in the elderly, creating challenges in their treatment.

Managing warfarin therapy in the elderly can be difficult because of warfarin's narrow therapeutic window, many drug interactions, need for routine laboratory monitoring, and dietary considerations. Direct oral anticoagulants alleviate some of these difficulties, but they have their own challenges. In many of the DOAC VTE trials, about 30% of the population was older than 65 years, and about 10%–20% was 75 years and older (Geldhof 2014). In many of the landmark AF clinical trials, over 50% of the population was older than 65 years, and 30%–40% of patients were 75 years and older.

A meta-analysis of key AF trials found that elderly patients randomized to DOACs had a reduced rate of stroke or systemic emboli compared with similar patients taking warfarin (RR 0.78; 95% CI, 0.68–0.78) and similar rates of major bleeding (RR 0.93; 95% CI, 0.74–1.17) (Ruff 2014). Individual trial

outcomes including elderly patients in AF are summarized in Table 2-8.

A similar meta-analysis of elderly patients in key VTE trials found that randomization to DOACs was associated with lower rates of both VTE recurrence (RR 0.55; 95% CI, 0.38–0.82) and major bleeding (RR 0.39; 95% CI, 0.17–0.90) (Table 2-9) (Geldhof 2014). However, Hokusai-VTE was not included in the major bleeding results for the meta-analysis because these results were unavailable. Although different DOACs cannot be compared directly, the authors note that elderly patients appear to have a greater safety benefit with apixaban and rivaroxaban over warfarin than those treated with dabigatran. Given that the meta-analysis was based on subgroup populations, the authors state that the results should be interpreted with caution.

Two additional meta-analyses of VTE and AF trials showed that DOACs have at least equal efficacy for VTE and AF in elderly patients (Sharma 2015; Sardar 2014b). Overall, DOACs did not lead to higher rates of major or clinically relevant bleeding than conventional therapy in elderly patients with VTE and AF (Sardar 2014b). Comorbidities in elderly patients should be considered when selecting anticoagulant therapy, and specific bleeding risks should be considered on an individual patient basis.

Table 2-8. Outcomes of Patients ≥ 75 years in Key AF Clinical Trials

Trial	DOAC Treatment	Stroke or Systemic Embolism			Major Bleeding		
		DOAC (%)	Warfarin (%)	OR (95% CI)	DOAC (%)	Warfarin (%)	OR (95% CI)
RE-LY	Dabigatran ^a	2.8	4.3	0.66 (0.49–0.90)	10.6	9	1.20 (0.98–1.46)
ROCKET-AF	Rivaroxaban	4	4.9	0.80 (0.63–1.02)	7.6	6.6	1.15 (0.93–1.42)
ARISTOTLE	Apixaban	2.8	3.9	0.71 (0.53–0.95)	5.3	7.9	0.65 (0.53–0.81)
AVERROES ^b		2.2 ^b	6.7 ^b	0.31 (0.19–0.52) ^b	2.9 ^b	2.4 ^b	1.18 (0.67–2.06) ^b
ENGAGE	Edoxaban	4.8 ^c	5.9	0.81 (0.65–1.03)	7.5 ^c	9.1	0.81 (0.67–0.98)
AF TIMI-48		6.6 ^d	5.9	1.12 (0.9–1.39)	4.3 ^d	9.1	0.46 (0.38–0.57)

^aDabigatran 150 mg BID cohort.

^bIn all trials, warfarin was the control cohort, except for the AVERROES, in which the control cohort was aspirin; major or clinically relevant bleeding reported, includes only patients > 75.

^cEdoxaban 60 mg cohort.

^dEdoxaban 30 mg cohort.

Information from: Sardar P, Chatterjee S, Chaudhari S, et al. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc* 2014;62:857-64; Sharma M, Cornelius VR, Patel JP, et al. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation* 2015;132:194-204.

DOSING AND MANAGEMENT OF DOACS IN SPECIAL POPULATIONS

Effect of Body Weight on Pharmacokinetics

Body weight is an important consideration for anticoagulation selection and dosing. Pharmacokinetic studies suggest that aside from edoxaban, body weight alone has a modest impact on pharmacokinetic parameters for rivaroxaban and

apixaban, with uncertain clinical significance (Reilly 2014; Upreti 2013; Kubitza 2007). As such, edoxaban is the only DOAC that requires a dose adjustment for weight alone in VTE treatment.

In a RE-LY subanalysis, weight was a significant predictor of dabigatran trough concentrations but not an independent risk factor for stroke or bleeding. By comparison, age, CrCl,

Table 2-9. Outcomes of Patients ≥ 75 Years in Key VTE Trials

Trial	DOAC Treatment	Efficacy			Major Bleeding		
		DOAC (%)	Warfarin (%)	RR (95% CI)	DOAC (%)	Warfarin (%)	RR (95% CI)
RE-COVER I ^a RE-COVER II ^a	Dabigatran	1.2	1.8	0.65 (0.17–2.45)	3.5	3.8	0.91 (0.37–2.19)
EINSTEIN DVT EINSTEIN PE	Rivaroxaban	2.3	3.7	0.62 (0.33–1.17)	1.2	4.5	0.27 (0.13–0.59)
AMPLIFY	Apixaban	1.8	3.6	0.50 (0.21–1.20)	1.0	4.3	0.23 (0.08–0.65)
Hokusai-VTE	Edoxaban	2.5	5.0	0.50 (0.27–0.94)	12.5 ^b	15.1 ^b	0.83 (0.62–1.12)

^aAge for analysis was > 75, not ≥ 75.

^bMajor and clinically relevant nonmajor bleeding.

Information from: Geldhof V, Vandenbrielle C, Verhamme P, et al. Venous thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants. *Thromb J* 2014;12:21.

and sex affected both trough concentrations and stroke and bleeding risk (Reilly 2014). In a pooled post hoc analysis of three trials (n=5686) assessing dabigatran compared with enoxaparin for VTE prophylaxis after orthopedic surgery, rates of VTE or VTE-related mortality were lower with dabigatran in the normal BMI group (greater than 20–25 kg/m²) and similar in the pre-obesity (BMI greater than 25–30 kg/m²) and obesity (BMI greater than 30 kg/m²) groups (Eriksson 2012). Rates of major bleeding were similar across all subgroups. These results suggest that dabigatran's efficacy and safety is minimally affected by body weight.

In a pooled analysis of the EINSTEIN trials, fragile patients (older than 75 years, CrCl less than 50 mL/min, or weight of 50 kg or less; n=1573) had similar rates of VTE occurrence and a greater reduction in major bleeding compared with non-fragile patients (interaction p=0.01) (Prins 2013). However, only 107 patients (6.8%) weighed 50 kg or less, making generalization difficult. Neither the EINSTEIN trials nor the ROCKET-AF trial found a relationship between weight or BMI and clinical outcomes in rivaroxaban compared with control (Morrill 2015). Using the prespecified dose adjustments, neither studies of apixaban (ARISTOTLE and ADVANCE) nor studies of edoxaban (ENGAGE-AF TIMI 48) noted an effect of weight on clinical outcomes (Morrill 2015).

Overall, these results suggest that clinical outcomes with DOACs are minimally affected by obesity compared with warfarin. However, because many of these trials used cutoffs such as weight 120 kg or BMI 30 kg/m², it is difficult to extrapolate these results to patients with significantly higher weight or BMI values (Morrill 2015).

The International Society on Thrombosis and Haemostasis recommends standard DOAC dosing in patients with a BMI of 40 kg/m² or less and weight of 120 kg or less; these authors suggest that a vitamin K antagonist (VKA) should be used in preference to DOACs in patients whose values are outside this range because few such patients were included in clinical trials (Martin 2016). The authors further suggest that medication-specific peak and troughs be used in such patients receiving DOACs; however, this may be challenging because no standard assays or ranges currently exist.

Valvular Disease

Although many large-scale clinical trials have assessed the safety and efficacy of DOACs in nonvalvular AF and VTE, available data are relatively limited in patients with valvular heart disease (VHD).

Mechanical Heart Valves

The RE-ALIGN trial (n=252) included patients undergoing mechanical aortic valve replacement or mechanical mitral valve replacement (MVR) and patients with a mechanical MVR at least 3 months prior (Eikelboom 2013). According to pharmacokinetic models, dabigatran was titrated for a goal trough plasma concentration of 50 ng/mL or greater. The

study was terminated prematurely because of excess bleeding and thrombotic complications in the dabigatran group. Of the patients randomized to dabigatran, 70% were at an intermediate or high risk of thromboembolic complications, 67% had a mechanical aortic valve replacement, and 29% had a mechanical MVR. The dabigatran group had therapeutic concentrations 86% of the time, compared with a percent time in therapeutic range of 49%–51% for the warfarin group. Although mortality was similar in both groups, randomization to dabigatran was associated with a nonsignificant increased risk of death, stroke, systemic embolism, or myocardial infarction (p=0.11) and an increased risk of any bleeding (HR 2.45; 95% CI, 1.23–4.86; p=0.01). Rates of major bleeding were similar, and all cases occurred within 1 week of cardiac surgery. Dabigatran concentrations were not associated with clinical events.

On the basis of the RE-ALIGN trial results, professional guidelines recommend against the use of dabigatran in patients with mechanical valves (January 2014). Although no direct comparisons between other DOACs and warfarin are available, it is prudent to avoid all DOACs in patients with mechanical valves at this time.

Valvular AF

Historically, the term *valvular AF* has denoted patients with AF and rheumatic heart disease (usually moderate to severe mitral stenosis [MS]) and/or prosthetic heart valves. The combination of MS and AF is particularly challenging because MS creates low flow in the left atrium, further increasing thrombotic risk (De Caterina 2014). Although patients with MS were mostly excluded from nonvalvular AF trials, several patients had other forms of VHD (Table 2-10).

In general, rates of stroke and systemic embolism between DOACs and warfarin were similar in patients with and without VHD compared with the overall results (interaction p=NS for all DOACs vs. warfarin). Although the presence of VHD did not affect the rates of major bleeding with either apixaban or dabigatran compared with warfarin (interaction p=NS for each), rivaroxaban was associated with an increased rate of major bleeding and major and nonmajor clinically relevant bleeding in patients with VHD. Rates of intracranial hemorrhage were similar with all DOACs and warfarin. Given these results, it may be prudent to avoid rivaroxaban in patients with VHD, when possible, because of the increased risk of major bleeding. No data concerning edoxaban in VHD are currently available.

Because forms of VHD other than MS do not typically create low-flow states in the left atrium and do not further increase the risk of thrombosis in AF, there is little reason to suspect that DOACs are less efficacious in patients with AF and VHD than in those without VHD; the results of substudies conducted in major AF trials support this hypothesis (De Caterina 2014). It is uncertain whether DOACs provide comparable benefit in AF and bioprosthetic heart valves or MS; however, a single-center, retrospective study found fairly low

Table 2-10. Summary of DOACs in VHD in Key AF Trials

	RE-LY (n=18,113)	ROCKET-AF (n=14,171)	ARISTOTLE (n=18,201)
Comparator	Dabigatran	Rivaroxaban	Apixaban
VHD, n (%) ^a	3950 (21.8)	2003 (14.1)	4808 (26.4)
Mitral regurgitation, n (%)	3101 (78.5)	1756 (89.6)	3526 (73.3)
Aortic regurgitation, n (%)	817 (20.7)	486 (24.8)	887 (18.4)
Aortic stenosis, n (%)	471 (11.9)	215 (11)	384 (8.0)
Stroke and systemic embolism ^{b,c}	VHD: 0.59 (0.37–0.93) No VHD: 0.67 (0.52–0.86); p=NS	VHD: 0.83 (0.55–1.27) No VHD: 0.89 (0.75–1.07); p=0.76	VHD: 0.70 (0.51–0.97) No VHD: 0.84 (0.67–1.04); p=0.38
Major bleeding ^{b,c}	VHD: 0.89 (0.68–1.16) No VHD: 0.99 (0.83–1.17); p=NS	VHD: 1.56 (1.14–2.14) No VHD: 0.98 (0.84–1.15) p=0.010	VHD: 0.79 (0.61–1.04) No VHD: 0.65 (0.55–0.77); p=0.23

^aPatients could have more than one type of VHD.

^bRefers to the comparison of DOAC with warfarin specifically in patients with VHD; numbers represented as HR (95% CI); interaction p value.

^cDabigatran 150 mg vs. warfarin.

NS = not significant; VHD = valvular heart disease.

Information from: Ezekowitz MD, Parise H, Nagarakanti R, et al. Comparison of dabigatran versus warfarin in patients with atrial fibrillation and valvular disease: the RELY trial. *J Am Coll Cardiol* 2014;63:A325; Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J* 2014;35:3377-85; Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation* 2015;132:624-32.

event rates in patients with bioprosthetic valves who were prescribed DOACs a mean of 990 days after surgery (Yadlapati 2016). No data are currently published regarding DOACs in patients with a transcatheter aortic valve replacement.

Use of DOACs in Patients Taking Antiplatelets

Treatment of patients requiring both OAC therapy and dual antiplatelet therapy (DAPT) has long been challenging. Most DAPT trials have excluded OAC, and most OAC trials have excluded DAPT. As such, professional guidelines have historically been vague regarding optimal management of this situation. Incorporation of potent P2Y₁₂ inhibitors (e.g., prasugrel, ticagrelor) and DOACs creates additional uncertainty because most “triple-therapy” (concomitant OAC and DAPT) trials specifically use aspirin, clopidogrel, and warfarin.

The WOEST trial enrolled patients (n=563) requiring long-term OACs who underwent acute percutaneous coronary intervention; all patients received warfarin and clopidogrel and were randomized to aspirin or placebo (Dewilde 2013). The most common OAC indication was AF (69%), 25%–30% of patients had an acute coronary syndrome, and 65% received a drug-eluting stent (DES). Over a median of 365 days, the primary end point of any bleeding occurred in 19.4% and 44.4% of

patients in the double- and triple-therapy groups, respectively (HR 0.36; 95% CI, 0.26–0.50; p<0.0001). Rates of TIMI major bleeding were similar between groups (p=0.159), but BARC type 3 bleeding was lower in the double-therapy group (HR 0.49; 95% CI, 0.28–0.86; p=0.011). Although not powered to definitively assess ischemic end points, double therapy was surprisingly associated with a reduction in all-cause mortality (HR 0.39; 95% CI, 0.16–0.93; p=0.027); rates of myocardial infarction, target-vessel revascularization, stroke, and stent thrombosis were comparable (Dewilde 2013). Similar results occurred in a large, nationwide cohort study (n=11,480), in which triple therapy was associated with higher bleeding rates and similar thromboembolic risk compared with warfarin and a single antiplatelet (Lamberts 2012).

Similarly, the PIONEER AF-PCI trial randomized patients (n=2124) with AF undergoing percutaneous coronary intervention at 1:1:1 to receive rivaroxaban 15 mg daily and a P2Y₁₂ inhibitor (group 1), rivaroxaban 2.5 mg twice daily and DAPT (group 2), or warfarin and DAPT (group 3). Clinicians pre-specified P2Y₁₂ inhibitor selection and DAPT duration (1, 6, or 12 months). Most patients received clopidogrel (94%), 52% presented with acute coronary syndrome, 30% total had an acute myocardial infarction, and 66% received a DES. Of note,

baseline characteristics differed across DAPT duration strata because DAPT duration was not randomized. At 12 months, the primary safety end point of clinically significant bleeding occurred in 16.8% (group 1), 18.0% (group 2), and 26.7% (group 3) (group 1 vs. group 3 HR 0.59; 95% CI, 0.47–0.76; $p < 0.001$ and group 2 vs. group 3 HR 0.63; 95% CI, 0.50–0.80; $p < 0.001$). Rates of TIMI major and minor bleeding were similar in all groups; exploratory end points of International Society on Thrombosis and Haemostasis major bleeding ($p = 0.013$) and GUSTO severe bleeding ($p = 0.012$) were both lower in group 1 than in group 3. Although rates of thromboembolic events were similar between groups, the trial was underpowered (11.4% power to detect a 15% difference) to assess these end points (Gibson 2016).

To investigate different durations of triple therapy, the ISAR-TRIPLE trial randomized patients ($n = 614$) requiring OAC and undergoing percutaneous coronary intervention to either a 6-week or a 6-month course of clopidogrel; all patients received aspirin and VKA (Fiedler 2015). The most common indication for OAC was AF or atrial flutter (82.7%–85%), and about 69% of patients presented with stable angina; almost all patients received a DES. Rates of death, myocardial infarction, stent thrombosis, or major bleeding and rates of TIMI major bleeding were similar at 9 months and between 6 weeks and 9 months. However, any BARC bleeding was lower between 6 weeks and 9 months in the 6-week group (HR 0.68; 95% CI, 0.47–0.98; $p = 0.04$) (Fiedler 2015).

In the RE-LY trial, 6952 patients (38.4%) received antiplatelets; 5789 (83.3%) took aspirin alone, and 812 (4.5%) took DAPT (Dans 2013). In the dabigatran 150-mg and warfarin groups, the reduction in stroke and systemic embolism was similar, regardless of antiplatelet use (interaction $p = 0.058$), though dabigatran's benefit appeared attenuated with antiplatelets. Similarly, stroke reduction was greater in patients not taking antiplatelets (HR 0.50; 95% CI, 0.36–0.70) than in those taking antiplatelets (HR 0.81; 95% CI, 0.59–1.10; interaction $p = 0.043$), further suggesting the attenuation of benefit with antiplatelets. Rates of hemorrhagic stroke (interaction $p = 0.56$) and major bleeding (interaction $p = 0.875$) were unaffected. Patients taking DAPT had higher rates of major bleeding than those taking a single antiplatelet (p for trend < 0.001), but relative increases were consistent across all dabigatran and warfarin doses. These results highlight the increased bleeding risk with antiplatelet therapy but suggest that the increased risk is similar with dabigatran and warfarin. However, the merits of dabigatran in patients with acute coronary syndromes and AF remain unknown.

Regarding other agents, the ROCKET-AF, ARISTOTLE, RE-COVER, AMPLIFY, and Hokusai-VTE trials excluded patients taking DAPT, whereas the AVERROES trial included only a few patients taking clopidogrel. The EINSTEIN trials allowed patients to receive DAPT, but a subgroup analysis has not been published, to our knowledge. Taken together,

relatively few data are available regarding DOACs compared with warfarin in patients being considered for triple therapy.

The 2014 AHA-ACC-HRS guidelines for management of atrial fibrillation state that it may be reasonable to use clopidogrel with an OAC and without aspirin in patients with a recent coronary revascularization and AF at an elevated stroke risk (class IIb, level of evidence B). The guidelines make no recommendations regarding the choice of anticoagulant. Authors of the 2016 ACC-AHA focused update on DAPT duration do not make specific recommendations regarding triple therapy, but they do summarize previously published recommendations from various sources; recommendations include using validated risk predictors to assess ischemic and bleeding risk, minimizing triple-therapy duration, considering an INR target of 2.0–2.5 for warfarin, using clopidogrel as the P2Y₁₂ inhibitor of choice, using low-dose (100 mg or less daily) aspirin, and using proton pump inhibitors (PPIs) in patients with a history of a GIB and state that it is reasonable to use PPIs in patients at risk of a GIB. Although the combination of clopidogrel and warfarin has been studied the most, use of a DOAC in place of warfarin in patients requiring double or triple therapy may also be reasonable (Levine 2016; January 2014).

LABORATORY MONITORING

One touted advantage of DOACs is that laboratory monitoring is not routinely recommended. However, in some scenarios, monitoring is clinically relevant (Burnett 2016; Cuker 2014). In patients with active bleeding, understanding whether a DOAC is present with a qualitative assay may be helpful. Conversely, in suspected treatment failure, a quantitative analysis may guide therapeutic adjustments. If measurement of a DOAC is clinically indicated, recent guidelines suggest use of assays that are readily available and validated (either locally or in a reference laboratory) (Burnett 2016). Suggestions for laboratory monitoring are outlined in Table 2-11.

Unlike with warfarin dosing, the timing of assays in relation to DOAC dosing is important, given the comparatively short half-life of the DOACs. For instance, aPTT and PT are not sensitive for dabigatran and may be normal at trough concentrations. Dabigatran monitoring is more reliable with dilute thrombin time (DTT) or ecarin-based assays because these are quantifiable and have more linearity (Cuker 2014). Agent-specific anti-factor Xa (anti-Xa) concentrations are most effective for rivaroxaban, apixaban, and edoxaban.

BLEEDING MANAGEMENT

Bleeding Management: Factor Products

Common comorbidities in ICU patients contribute to an increased risk of pronounced anticoagulant effects with both DOACs and traditional anticoagulants. Some studies suggest that patients who have major bleeding events with DOACs will need less blood or factor products than those with bleeding related to warfarin (Piccini 2014; Majeed 2013).

Table 2-11. Suggestions for Laboratory Measurements of DOACs

	Determine If Medication Is Present		Estimated Therapeutic Medication Levels	Determine If Medication Levels Are Above Therapeutic	
	Suggested Test	Interpretation		Suggested Test	Interpretation
Dabigatran	TT	Normal levels likely exclude clinically relevant medication levels	DTT, ECA, ECT	aPTT, DTT, ECA, ECT	Normal aPTT excludes excess medication; only TT, ECA, and ECT are quantitative measures
Rivaroxaban	Anti-Xa		Anti-Xa	Anti-Xa, PT	Normal PT excludes excess medication; only anti-Xa is suitable for quantitative measure
Apixaban	Anti-Xa		Anti-Xa	Anti-Xa	Normal PT does NOT exclude excess medication; only anti-Xa is suitable for quantitative measure
Edoxaban	Anti-Xa		Anti-Xa	Anti-Xa, PT	Normal PT excludes excess medication; only anti-Xa is suitable for quantitative measure

ECA = ecarin chromogenic assay; ECT = ecarin clotting time.

Information from: Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis* 2016;41:206-32; Cuker A, Siegal DM, Crowther MA, et al. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014;64:1128-39.

Understanding strategies to manage bleeding is paramount to patient care, but consideration must also be given to the underlying thromboembolic conditions for which the anticoagulant was initially intended. Strategies for anticoagulant reversal are not without adverse effects and may alter the risk from bleeding to thrombosis.

Regardless of the specific DOAC used, management of suspected bleeding typically begins with assessing hemodynamic status, identifying the source of bleeding, and determining the presence of a DOAC. Presence of a DOAC is determined according to time since last dose, end-organ function, coagulation parameters, and screening for medication interactions. This information helps estimate the continued duration of anticoagulant exposure. Subsequent steps in management will vary, depending on the severity of bleeding. For mild bleeding in a hemodynamically stable patient, withholding anticoagulation may be the only treatment necessary.

Moderate or severe bleeding may require supportive strategies such as resuscitation with intravenous fluid and blood products, mechanical compression, and/or surgical intervention (Box 2-1). Fresh frozen plasma (FFP) is not routinely recommended in DOAC reversal (Burnett 2016) because the amount of FFP needed to overwhelm the inhibition of factor Xa and thrombin would likely lead to adverse effects such as fluid overload. If anticoagulant ingestion occurred within the

previous 2 hours, oral activated charcoal might be an option. Activated charcoal reduced apixaban exposure by 50% and 28% when given 2 hours and 6 hours, respectively, after a single apixaban 20-mg dose in 18 healthy subjects (Wang 2014). Activated charcoal can be considered with rivaroxaban, but it may be of limited usefulness with its rapid gastric absorption (Frontera 2016).

Box 2-1. Supportive Strategies to Consider for the Management of Bleeding Associated with DOAC Use

- Anticoagulant withdrawal
- Local hemostatic measures
- Hemodynamic monitoring
- Mechanical compression or surgical intervention
- Hemodynamic support
- Fluid and blood product replacement

Information from: Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis* 2016;41:206-32; Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. *J Thromb Thrombolysis* 2015;39:395-402; Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016;24:6-46.

Table 2-12. Anticoagulant Reversal Strategies in Severe Bleeding

Anticoagulant	Primary Strategies for Consideration
Direct thrombin inhibitors	Dabigatran Idarucizumab 5 g IV (as two divided doses administered consecutively) Oral activated charcoal 50 g x 1 dose if ingestion within previous 2 hr Hemodialysis can be considered in acute renal failure
Factor Xa inhibitors	Rivaroxaban Apixaban Edoxaban 50 units/kg ^a of nonactivated four-factor PCC or 50 units/kg ^a of activated PCC Oral activated charcoal 50 g x 1 dose if ingestion within previous 2 hr

^aAlternative doses have also been proposed.

IV = intravenous(ly).

Information from: Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis* 2016;41:206-32; Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. *J Thromb Thrombolysis* 2015;39:395-402; Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016;24:6-46; Nutescu EA, Dager WE, Kalus JS, et al. Management of bleeding and reversal strategies for oral anticoagulants: clinical practice considerations. *Am J Health Syst Pharm* 2013;70:1914-29.

Although holding anticoagulation and/or activated charcoal may be useful in some situations, severe or life-threatening bleeding may require reversal of the anti-coagulant effect. Options for reversal include blood factor products such as nonactivated prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), and recombinant factor VIIa or use of a direct reversal agent, when available (summarized in Table 2-12).

Nonactivated PCCs are currently available as three-factor products containing factors II, IX, and X and low concentrations of factor VII (Bebulin and Profilnine) and four-factor products containing factors II, VII, IX, and X (Kcentra). These nonactivated PCCs contain variable amounts of protein C and S. By comparison, aPCCs contain nonactivated factors II, IX, and X and activated factor VII (FEIBA). Reported thromboembolism risks are variable with PCCs but are estimated to be low (Frontera 2016; Siegal 2014). Using the lowest effective doses of PCCs and considering underlying thrombotic conditions can help minimize thromboembolic risk. Of note, clinicians should be aware that Bebulin and Kcentra contain heparin and are contraindicated in patients with a confirmed heparin allergy. Other factor products, including Profilnine and FEIBA, do not contain heparin. Although potentially useful, evidence for DOAC reversal with factor products is limited, given that much of the data involve improving coagulation parameters rather than clinical outcomes (Siegal 2014).

Bleeding Management: Reversal Agents for DOACs

Although many traditional anticoagulants have specific antidotes for reversing their anticoagulant effect, lack of direct reversal agents has limited DOAC use in some patients. Fortunately, idarucizumab was recently approved for dabigatran reversal, and other direct reversal agents for factor Xa inhibitors are currently in development (Table 2-13).

Idarucizumab is a humanized monoclonal antibody approved for reversal of dabigatran for emergency procedures or life-threatening bleeding. Idarucizumab binds to both free and thrombin-bound dabigatran with an affinity 350 times that of thrombin. Idarucizumab is highly specific to dabigatran and does not bind to other thrombin substrates. Idarucizumab is dosed as a 5-g intravenous bolus (administered as two doses of 2.5 g no more than 15 minutes apart). After an initial dose of idarucizumab 5 g, an additional dose of 5 g can be considered if coagulation parameters are continually elevated, according to manufacturer recommendations. Idarucizumab clearance may be impaired in renal dysfunction, leading to AUC increases of 43.5% and 83.5% for mild (CrCl 60–90 mL/min) and moderate (30–60 mL/min) renal impairment, respectively; no dosing adjustment is recommended by the manufacturer. Six hours after a 5-g intravenous dose of idarucizumab, about 32% was found in the urine and less than 1% was found after 18 hours; the remainder was assumed to be eliminated through protein metabolism. Idarucizumab has a small volume of distribution (8.9 L) and therefore primarily stays within the blood.

The RE-VERSE AD trial is an ongoing prospective cohort study assessing idarucizumab's effect on reversing dabigatran (Pollack 2015). An interim analysis of the first 90

Table 2-13. Key Characteristics of Select Anticoagulant Reversal Agents

	Idarucizumab	Andexanet Alfa (PRT064445)	Ciraparantag (PER977)
Availability	FDA approved	Orphan drug status	Fast track status
Potential anticoagulants to be reversed	Dabigatran	Direct and indirect factor Xa inhibitors, LMWH	Direct thrombin inhibitors, factor Xa inhibitors, heparins (LMWH and unfractionated)
Structure	Humanized monoclonal antibody fragment (Fab)	Recombinant modified human factor Xa decoy protein	Synthetic molecule
Mechanism	Noncompetitive binding to dabigatran	Competitive binding to factor Xa inhibitors	Binds to direct thrombin inhibitors, factor Xa inhibitors, heparins through hydrogen bonds
Dosing	5 g IV (as two divided doses administered consecutively)	400–800 mg IV with or without 4- to 8-mg/min infusion for 2 hr ^a	100–300 mg IV ^a
Time to response	Immediate	2–5 min	10–30 min
Half-life	47 min (initial); 10.3 hr (terminal)	1 hr	1.5 hr

^aFDA-approved dosing has not yet been established; dosing listed reflects current studied doses.

LMWH = low-molecular-weight heparin.

Information from: manufacturers' package inserts; Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. *J Thromb Thrombolysis* 2015;39:395-402; Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013;19:446-51; Perosphere and Daiichi Sankyo Enter into a Clinical Trial Agreement to Evaluate the Efficacy and Safety of PER977 to Reverse the Anticoagulant Activity of the Investigational, Oral, Once-Daily Factor Xa Inhibitor Edoxaban. Available at www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/005954.html. Accessed May 20, 2016; Smythe MA, Trujillo T, Fanikos J. Reversal agents for use with direct and indirect anticoagulants. *Am J Health Syst Pharm* 2016;73(10 suppl 2):S27-S48.

patients included patients requiring dabigatran reversal in either life-threatening bleeding (n=51) or need for emergency surgery (n=39). Most patients (96%) were receiving dabigatran for AF; 64% of patients were taking dabigatran 110 mg twice daily, and 13% had a CrCl less than 30 mL/min. Patients received idarucizumab as two 2.5-g boluses, and all but two patients were followed for at least 1 month or until death. The primary outcome, percent reversal of dabigatran, was assessed by DTT and ECT. Among patients with elevated ECT and DTT, the median maximal reversal was 100% after the first idarucizumab infusion. Median time for cessation of bleeding was 11.4 hours in the bleeding cohort (25 patients assessed), and 92% of patients achieved intraoperative hemostasis in the surgery cohort (36 patients assessed). Overall, death occurred in 18 patients, nine in each of the cohorts, including five thrombotic events and five fatal bleeding events. Of interest, dabigatran concentrations increased after the idarucizumab infusion at 12 hours (6 patients) and 24 hours (16 patients). Because dabigatran has a large volume of distribution (50–70 L), according to the Pradaxa package insert,

and distributes between the blood and tissues, this may reflect dabigatran redistribution.

Andexanet alfa (PRT064445) is a recombinant modified human factor Xa decoy protein that binds factor Xa inhibitors, restores endogenous factor Xa activity, and reduces anticoagulant effect. Although andexanet mimics factor Xa, it is catalytically inactive and has no anticoagulant properties (Lu 2013). Andexanet received breakthrough therapy designation from the FDA in November 2013 and orphan drug status in February 2015.

The ANNEXA-A and ANNEXA-R were two parallel, double-blind trials that enrolled healthy volunteers (n=145) receiving either apixaban or rivaroxaban and randomized them to receive andexanet (n=101) or placebo (n=44) (Siegal 2015b). Subjects received apixaban 5 mg twice daily for 3.5 days or rivaroxaban 20 mg daily for 4 days; andexanet or matching placebo was then given as a 400- or 800-mg intravenous bolus with or without a 2-hour infusion of 4 or 8 mg/minute (with the lower doses used for apixaban and higher doses for rivaroxaban, respectively). In both the apixaban and rivaroxaban groups, andexanet significantly reduced anti-Xa activity

by about 90%, compared with a 20% reduction in the placebo arms. The reversal of anti-Xa activity persisted for 1–2 hours after completion of the andexanet infusion before returning to concentrations similar to those in the placebo group. This time interval is consistent with andexanet's half-life of about 1 hour. Of importance, because this trial enrolled healthy volunteers receiving a short course of anticoagulation, it is difficult to extrapolate these results to unstable patients requiring emergency reversal. However, subsequent trials have further assessed reversal of apixaban and rivaroxaban, and other data show that andexanet can reverse fondaparinux and enoxaparin (Lu 2013).

A more recent interim analysis of the ANNEXA-4 trial describes andexanet use in 67 patients with acute major bleeding. All patients received apixaban (n=31), rivaroxaban (n=32), or enoxaparin (n=4) within 18 hours of presentation (Connolly 2016). About 70% of patients had AF, and bleeding events were primarily GI (49%) and intracranial (42%). Andexanet was administered as a 400- or 800-mg bolus, followed by a 2-hour infusion of 4 or 8 mg/minute (the lower doses were used if apixaban or rivaroxaban was taken more than 7 hours before andexanet, and higher doses were used if enoxaparin, edoxaban, or rivaroxaban was taken 7 hours or less before andexanet). The mean time from ED presentation to andexanet administration was 4.8 hours. Efficacy outcomes were analyzed in the 47 patients with baseline anti-Xa activity of 75 ng/mL or greater (or 0.5 IU/mL or greater for enoxaparin). After the andexanet bolus, anti-Xa activity decreased by 89% and 93% from baseline in patients receiving rivaroxaban and apixaban, respectively. When measured 4 hours after completion of andexanet, there was a partial return to baseline anti-Xa activity with a reduction of only 39% and 30% from baseline for rivaroxaban and apixaban, respectively. Clinically, 79% of patients were determined to have good or excellent hemostasis 12 hours after receiving andexanet, despite a rebound in anti-Xa activity. Thrombotic outcomes (assessed in all patients) occurred in 12 patients (18%), with some having several events, and death occurred in 10 patients (15%). Of those with a thrombotic event, anticoagulation was reinitiated in only one patient before the event. Clinical pharmacists must be thoughtful when weighing the risks and benefits to determine the appropriate time interval for reinitiating anticoagulation.

Ciraparantag (PER977) is an experimental agent that may reverse direct thrombin inhibitors, factor Xa inhibitors, and heparins. A double-blind, placebo-controlled trial randomized healthy patients (n=80) to receive ciraparantag 25 mg, 100 mg, or 300 mg intravenous bolus or placebo 3 hours after receiving a single dose of edoxaban 60 mg (Ansell 2014). Whole blood clotting time decreased to 10% of baseline within 10 minutes of receiving ciraparantag 100 mg or 300 mg compared to within 12–15 hours in the placebo group; this reduction remained at 24 hours in patients receiving ciraparantag 100 mg or 300 mg. Although not yet FDA approved, ciraparantag received fast track status in April 2015 (Perosphere 2016).

Bleeding Management: Summary

According to published consensus recommendations, nonactivated four-factor PCCs or aPCCs should be the initial strategy to reverse factor Xa inhibitors, whereas idarucizumab should be considered the first-line agent for dabigatran reversal over PCCs and aPCCs (Burnett 2016; Frontera 2016; Siegal 2015a). Recombinant factor VIIa (NovoSeven RT) monotherapy is not considered a first-line reversal strategy for DOACs because four-factor PCCs and aPCCs have better reversal of coagulation parameters (Frontera 2016). Because four-factor PCCs contain factor VII, the strategy for giving additional recombinant factor VIIa (NovoSeven RT) after administration of a four-factor PCC is unclear. In addition, recombinant factor VIIa may be associated with more thrombotic complications than PCCs and aPCC (Dentali 2011; Levi 2010). Hemodialysis may also be an option for dabigatran removal, given that a 4-hour session removes about 50% of dabigatran. However, dabigatran concentrations may rebound after hemodialysis due to the large volume of distribution of this agent (Chang 2013; Singh 2013). Hemodialysis is not expected to be useful for oral factor Xa inhibitors, likely due to protein binding (Nutescu 2013).

CONCLUSION

In conclusion, DOACs are a reasonable alternative to warfarin in many patients. However, although results from key clinical trials have mostly been positive, clinicians must continue to use caution in patients with severe renal impairment, moderate or severe hepatic dysfunction, and extreme body weight. Direct oral anticoagulants generally appear safe in elderly patients and may be reasonable alternatives to warfarin in patients requiring dual or triple therapy. Direct oral anticoagulants should be avoided in patients with mechanical heart valves. Uncertainty exists regarding the usefulness and standardization of DOAC laboratory monitoring. The advent of new reversal agents (e.g., idarucizumab, andexanet alfa) offers treatment options in emergencies.

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Practice Points

- When compared with warfarin in patients with AF, dabigatran and apixaban were associated with reductions in stroke and systemic embolism, whereas rivaroxaban and edoxaban were noninferior. Both apixaban and edoxaban were associated with reductions in major bleeding, whereas dabigatran and rivaroxaban were noninferior.
- All four DOACs were associated with reductions in intracranial hemorrhage; apixaban was also associated with similar rates of GIB, whereas the others were associated with increased rates of GIB.
- For patients with VTE, compared with standard therapy, all four DOACs were noninferior for the primary thrombotic end point. Both rivaroxaban and apixaban were also associated with reductions in major bleeding.
- DOACs appear to have similar or improved thrombotic clinical end points and major bleeding compared with warfarin for mild-moderate renal impairment. Clinicians should use caution with DOACs in severe renal impairment.
- Dabigatran and apixaban may be considered in moderate hepatic impairment; rivaroxaban and edoxaban should be avoided in moderate-severe hepatic impairment.
- DOACs do not appear to disproportionately increase the risk of bleeding in elderly patients.
- Efficacy and safety of DOACs appear minimally affected by obesity; however, little evidence exists regarding DOACs in patients with a BMI greater than 40 kg/m² or weight greater than 120 kg.
- DOACs should be avoided in patients with mechanical heart valves but may be considered in other types of VHD (though limited data exist).
- Clopidogrel is the preferred P2Y₁₂ inhibitor in patients requiring triple therapy; most triple-therapy trials have used warfarin, but DOACs may be reasonable alternatives to warfarin in patients requiring dual or triple therapy.
- Thrombin time (dabigatran) or agent-specific anti-Xa concentrations (rivaroxaban, apixaban, edoxaban) may be useful in certain situations, but standard therapeutic ranges have not been identified.
- Idarucizumab is the only available DOAC reversal agent at this time and is used only for dabigatran. PCCs and aPCC may be considered for severe bleeding with other DOACs.

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Self-Assessment Questions

21. A 55-year-old woman has newly diagnosed atrial fibrillation (AF). Her medical history is significant for hypertension, asthma, hypothyroidism, and an upper GI bleed (GIB) 2 years ago. Her CrCl is 95 mL/min. The decision is made to initiate anticoagulation; she wants to avoid frequent INR testing, but she is willing to take a direct oral anticoagulant (DOAC). Which one of the following is best to recommend for this patient?
- Dabigatran 150 mg twice daily
 - Rivaroxaban 20 mg every evening with food
 - Apixaban 5 mg twice daily
 - Edoxaban 30 mg daily
22. A 72-year-old man (weight 55 kg) was treated with warfarin 15 years ago for the management of an unprovoked deep venous thrombosis (DVT). After a significant bleeding episode several years ago, warfarin was discontinued. However, he now presents with a new pulmonary embolism (PE). The patient is willing to try an oral anti-coagulant (OAC) again as long as it is not warfarin. In addition, he states that he would like to leave the hospital as soon as possible to return to his family and is not interested in outpatient injections. His medical history is significant for asthma, rheumatoid arthritis, diabetes, and depression. His SCr is 1.2 mg/dL; his CBC is within normal limits. Which one of the following regimens is best to recommend for this patient?
- Dabigatran 150 mg twice daily
 - Rivaroxaban 15 mg twice daily with food x 21 days; then rivaroxaban 20 mg daily with food
 - Apixaban 5 mg twice daily
 - Edoxaban 60 mg daily
23. A 65-year-old man with a history of hypertension, diabetes, and a mechanical aortic valve placed 9 months ago presents with new-onset AF. He has taken warfarin since his surgery, but he asks about transitioning to a non-warfarin OAC to eliminate INR monitoring. Having seen commercials for new medications, he wonders if he is a candidate. Which one of the following is the most appropriate OAC for this patient?
- Warfarin
 - Dabigatran
 - Rivaroxaban
 - Apixaban
24. A 77-year-old man (weight 68 kg) presents with new-onset AF. His medical history includes hypertension, diabetes, distant DVT (treated with warfarin 20 years ago), and moderate-severe aortic stenosis. His SCr is 2.10 mg/dL (CrCl 28 mL/min). Of note, the patient mentions he had significant difficulty maintaining therapeutic “warfarin levels” previously. Which one of the following is best to recommend for this patient?
- Rivaroxaban 20 mg every evening with food
 - Apixaban 5 mg twice daily
 - Apixaban 2.5 mg twice daily
 - Warfarin (goal INR 2–3)
25. A 65-year-old woman receiving hemodialysis is currently admitted to the cardiac ICU with new-onset AF. At present, she is hemodynamically stable. Which one of the following is best to recommend for this patient?
- Apixaban
 - Rivaroxaban
 - Edoxaban
 - Warfarin

Questions 26 and 27 pertain to the following case.

M.S. is a 55-year-old woman (height 65 inches, weight 60 kg) with newly diagnosed AF. Her medical history is significant for heart failure with reduced ejection fraction and hypertension. Her SCr is 1.7 mg/dL and her Hgb is 13 g/dL. M.S. is initiated on apixaban 2.5 mg twice daily.

26. Several months later, M.S. is admitted to the ICU with pneumonia. On day 2 of hospitalization, she is intubated and has a nasogastric tube for drug administration but is not currently receiving enteral nutrition. Her current weight is 59 kg; SCr is 1.9 mg/dL and Hgb is 12 g/dL. Which one of the following is the best option for continued anticoagulation in M.S.?
- Change apixaban to unfractionated heparin.
 - Change apixaban to dabigatran.
 - Continue apixaban.
 - Change apixaban to rivaroxaban.
27. On day 3 of hospitalization, M.S.’s renal function worsens because of suspected contrast-induced nephropathy. Her SCr is 5.0 mg/dL and Hgb is 7 g/dL. The team is discussing the possible need for hemodialysis. Which one of the following is best to recommend for M.S.?
- Change apixaban to rivaroxaban 15 mg daily.
 - Change apixaban to dabigatran 75 mg twice daily.
 - Continue apixaban at current dosing.
 - Discontinue apixaban.
28. An 81-year-old man (weight 59 kg) is admitted to the medical ICU for an acute PE. He was initiated on a heparin infusion 4 days ago. The team would like your recommendation for continued therapy. His CrCl is 40 mL/min, and he has Child-Pugh C hepatic impairment.

Which one of the following is best to recommend for this patient?

- A. Continue parenteral anticoagulation for 5 days; then begin dabigatran 150 mg twice daily.
 - B. Discontinue heparin and begin edoxaban 30 mg daily.
 - C. Discontinue heparin and begin apixaban 5 mg twice daily.
 - D. Discontinue heparin and begin rivaroxaban 15 mg twice daily.
29. A 54-year-old woman (weight 70 kg) presents with new-onset AF. Her medical history includes two drug-eluting stents (DESs) to her left anterior descending artery placed more than 24 months ago. Since then she has taken aspirin and clopidogrel. The interventional cardiologist wants a medication regimen to minimize bleeding risk because the patient will require long-term anticoagulation. The patient's laboratory test values include SCr 0.8 mg/dL and CBC within normal limits. Which one of the following is best to recommend for this patient?
- A. Aspirin 81 mg daily, clopidogrel 75 mg daily, and rivaroxaban 5 mg twice daily
 - B. Aspirin 81 mg daily, clopidogrel 75 mg daily, and dabigatran 150 mg twice daily
 - C. Aspirin 81 mg daily, clopidogrel 75 mg daily, and apixaban 5 mg twice daily
 - D. Clopidogrel 75 mg daily and warfarin (goal INR 2–3)

Questions 30 and 31 pertain to the following case.

V.W. is a 73-year-old man with a history of a three-vessel coronary artery bypass grafting, several prior myocardial infarctions with stent placement, heart failure with preserved ejection fraction, AF, three prior PEs, and a history of protein C and protein S deficiency. He presents with chest pain, nausea, and vomiting. V.W. is found to have an elevated troponin as well as T-wave inversions on ECG. He is given a diagnosis of a non-ST-segment elevation myocardial infarction and taken to the cardiac catheterization laboratory, where he receives two DES to his right coronary artery.

30. Which one of the following is the most appropriate antithrombotic regimen for V.W.?
- A. Aspirin 81 mg daily and prasugrel 10 mg daily
 - B. Aspirin 81 mg daily, clopidogrel 75 mg daily, and warfarin (goal INR 2–3)
 - C. Clopidogrel 75 mg daily and apixaban 5 mg twice daily
 - D. Aspirin 81 mg daily, ticagrelor 90 mg twice daily, and rivaroxaban 20 mg daily
31. Assume that V.W. has a history of a GIB and thrombocytopenia. Which one of the following is best to recommend for V.W.?

- A. Aspirin 81 mg daily, clopidogrel 75 mg daily, and warfarin (INR 2–3) for 6 weeks; then aspirin and warfarin alone
 - B. Aspirin 81 mg daily, clopidogrel 75 mg daily, and rivaroxaban 20 mg daily indefinitely
 - C. Aspirin 81 mg daily and clopidogrel 75 mg daily
 - D. Aspirin 81 mg daily and apixaban 5 mg twice daily
32. A 43-year-old woman (height 70 inches, weight 125 kg) presents with swelling in her left calf; she is found to have an acute DVT. Her medical history is significant only for asthma and seasonal allergies. Her SCr is 0.88 mg/dL; her CBC is within normal limits. Which one of the following is best to recommend for anticoagulation in this patient?
- A. Warfarin (goal INR 2–3) with a parental anticoagulant bridge for at least 5 days and until INR is therapeutic for 24 hours or more
 - B. Apixaban 5 mg twice daily
 - C. Rivaroxaban 15 mg twice daily with food x 21 days; then rivaroxaban 20 mg daily with food
 - D. Dabigatran 150 mg twice daily
33. A 55-year-old man (weight 70 kg) presents with palpitations and fatigue. The patient has a history of hypertension, coronary artery disease (last DES 3 years ago), diabetes, and moderate mitral regurgitation. His laboratory tests show SCr 0.72 mg/dL, CrCl 115 mL/minute, and CBC within normal limits. The patient is given a diagnosis of AF, and the team wants to initiate anticoagulation. He is willing to take an OAC but would like to avoid frequent laboratory monitoring, if possible. Given the presence of mitral regurgitation, which one of the following is the best antithrombotic regimen to recommend for this patient?
- A. Warfarin (goal INR 2–3)
 - B. Rivaroxaban 15 mg in the evening with a meal
 - C. Apixaban 5 mg twice daily
 - D. Edoxaban 60 mg daily
34. A 73-year-old woman (weight 50 kg) is given a diagnosis of a new PE. Her medical history includes osteoarthritis, hypothyroidism, and hypertension. Laboratory tests show SCr 0.6 mg/dL, CrCl 65 mL/minute, and CBC within normal limits. The patient is not interested in taking warfarin because of the need for regular INR monitoring; she would prefer to take as few pills as possible. Which one of the following is best to recommend for this patient?
- A. Dabigatran 150 mg twice daily (after 5–10 days of parental anticoagulation)
 - B. Rivaroxaban 15 mg twice daily with food x 21 days; then rivaroxaban 20 mg daily with food
 - C. Apixaban 5 mg twice daily
 - D. Edoxaban 60 mg daily (after 5–10 days of parenteral anticoagulation)

35. A 57-year-old man (weight 85 kg) was prescribed rivaroxaban 20 mg daily for AF. He presents to the ED 6 hours after accidentally ingesting five 20-mg tablets. No acute bleeding is noted. His blood pressure is 120/73 mm Hg, heart rate 78 beats/minute, SCr 0.9 mg/dL, Hgb 10 g/dL, and aPTT 70 seconds. His home drugs include lisinopril 10 mg daily, aspirin 81 mg daily, and carvedilol 6.25 mg twice daily. Which one of the following is best to recommend for this patient?
- Withhold next rivaroxaban dose.
 - Administer one dose of oral activated charcoal 50 g.
 - Administer 2 units of fresh frozen plasma (FFP).
 - Give 50 units/kg of nonactivated four-factor PCC.
39. A 67-year-old woman who was receiving edoxaban 60 mg daily before admission for AF is admitted with a GIB. Her Hgb is 6.7 g/dL, SCr 0.8 mg/dL, and PT 21 seconds. Her last edoxaban dose was about 8 hours before admission. Assuming the availability of all the options, which one of the following is best to recommend for this patient?
- Activated charcoal
 - Idarucizumab
 - Ciraparantag
 - Factor VIIa
40. A 90-year-old woman (weight 88 kg) is admitted to the medical ICU for a possible GIB. Before admission, she was receiving rivaroxaban 20 mg daily for a recent PE. Her last dose of rivaroxaban was 26 hours ago. Laboratory results show SCr 2.6 mg/dL, Hgb 8.1 g/dL, and bilirubin 0.3 mg/dL. The team would like to assess her current exposure to rivaroxaban. Which one of the following is best guidance to give this patient's care team?

Questions 36 and 37 pertain to the following case.

B.L. is an 81-year-old woman (weight 63 kg) who presents with GI discomfort; the team is concerned about a potential GIB. Her home drugs include dabigatran 150 mg twice daily for the treatment of a DVT (diagnosed 1 month ago), metoprolol tartrate 50 mg twice daily, omeprazole 20 mg daily, amiodarone 200 mg daily, and hydrochlorothiazide 25 mg daily. B.L.'s laboratory results show SCr 3.5 mg/dL and Hgb 9 g/dL.

36. Which one of the following is the best next step for B.L.?
- Administer idarucizumab 5 g intravenously.
 - Begin hemodialysis.
 - Administer 50 units/kg of aPCC.
 - Assess time of last dabigatran dose.
37. Six hours later, B.L. has repeat laboratory tests showing an Hgb of 6 g/dL and an SCr that has increased to 5.2 mg/dL. She has active hematemesis. Which one of the following is best to recommend for B.L.?
- Administer one dose of activated charcoal 50 g.
 - Begin hemodialysis.
 - Administer idarucizumab 5 g intravenously.
 - Administer 50 units/kg of aPCC.
38. A 73-year-old woman (weight 63 kg) presents with an intracranial hemorrhage after a mechanical fall. She was transferred from an outside hospital after receiving Kcentra 50 units/kg 24 hours ago. Before presenting at the outside hospital, she was receiving edoxaban 30 mg daily for AF, aspirin 81 mg daily, atorvastatin 40 mg daily, and allopurinol 100 mg daily. Her last dose of edoxaban was 48 hours ago. She is currently hemodynamically stable with no evidence of ongoing bleeding. Her Hgb is 8.5 mg/dL, SCr 3.5 mg/dL, and PT 10 seconds, and liver function tests are within normal limits. Which one of the following is best to recommend for this patient?
- Begin hemodialysis.
 - Give FEIBA 50 units/kg.
 - Give recombinant factor VIIa 20 mcg/kg.
 - No additional therapy is needed at this time.

- A normal PT excludes excess rivaroxaban.
- Administer FFP immediately.
- Given the estimated CrCl, it is safe to assume that the patient is no longer exposed to rivaroxaban.
- An anti-Xa for rivaroxaban will assess only qualitative amounts of rivaroxaban.

Learner Chapter Evaluation: Direct Oral Anticoagulants in Special Populations.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
 - Agree
 - Neutral
 - Disagree
 - Strongly disagree
18. The content of the chapter met my educational needs.
 19. The content of the chapter satisfied my expectations.
 20. The author presented the chapter content effectively.
 21. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
 22. The content of the chapter was objective and balanced.
 23. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
 24. The content of the chapter was useful to me.
 25. The teaching and learning methods used in the chapter were effective.
 26. The active learning methods used in the chapter were effective.
 27. The learning assessment activities used in the chapter were effective.
 28. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

29. Assess the risks and benefits of direct oral anticoagulants (DOACs) compared with traditional anticoagulants.
30. Design an appropriate DOAC regimen for patients with alterations in organ function.
31. Develop an evidence-based strategy for the management of DOACs in patients with selected comorbid conditions.
32. Design a treatment approach to manage bleeding complications associated with DOACs.
33. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
34. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 35–37 apply to the entire learning module.

35. How long did it take you to read the instructional materials in this module?
36. How long did it take you to read and answer the assessment questions in this module?
37. Please provide any additional comments you may have regarding this module:

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Volume Management in Acute Decompensated Heart Failure

By Abigail M. Cook, Pharm.D., BCPS; and Ian B. Hollis, Pharm.D., BCPS-AQ Cardiology

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LEARNING OBJECTIVES

1. Distinguish between hypervolemia, hypovolemia, and euvolemia in acute decompensated heart failure (ADHF) on the basis of hemodynamic parameters.
2. Evaluate the results of invasive monitoring to create a pharmacologic treatment plan to improve the hemodynamic status of a patient with ADHF.
3. Assess the role of intravenous vasodilators as add-on therapy for the management of hypervolemia in ADHF.
4. Evaluate the usefulness of vasopressin receptor antagonists in hypervolemic hyponatremia.
5. Devise a volume management strategy using ultrafiltration in ADHF.
6. Develop a patient-specific treatment plan for the management of hypervolemia in ADHF.

ABBREVIATIONS IN THIS CHAPTER

ADHF	Acute decompensated heart failure
BNP	B-type natriuretic peptide
CIV	Continuous intravenous infusion
CKD	Chronic kidney disease
CO	Cardiac output
CVP	Central venous pressure
eCrCl	Estimated creatinine clearance
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
IVB	Intravenous bolus
LOS	Length of stay
NT-proBNP	N-terminal pro B-type natriuretic peptide
PAC	Pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
SVR	Systemic vascular resistance
TTE	Transthoracic echocardiogram
UF	Ultrafiltration
UOP	Urinary output
VRA	Vasopressin receptor antagonist
WRF	Worsening renal function

[Table of other common abbreviations.](#)

INTRODUCTION

It is estimated that 5 million Americans older than 20 years have heart failure (HF); this number is expected to increase by 25% over the next 15 years (Go 2013). Of particular importance is the distinction between HF with reduced ejection fraction (HFrEF) (40% or less, formerly called *systolic HF*) and HF with preserved ejection fraction (HFpEF) (50% or greater, formerly *diastolic HF*) (Yancy 2013). Patients with an ejection fraction (EF) of 41%–49% may have either “borderline” HFpEF (patients with HFpEF physiology with slightly lower EF) or “improved” HFrEF (patients with HFrEF with improvement in EF in response to treatment). Although the etiologies of these types of HF may vary, they have the common clinical presentation of impaired cardiac output (CO), often coupled with issues related to fluid overload. Although patients with HFrEF often tolerate very aggressive diuresis (as described in the following), patients with HFpEF may have some concomitant degree of preload dependence, often requiring a slower and more careful approach to diuresis.

Many patients with these types of HF will have rapid worsening of their clinical condition that requires hospitalization. This acute decompensated heart failure (ADHF) presents as a group of signs and symptoms such as shortness of breath, fluid overload, and generalized fatigue, often with concomitant hyper- or hypotension (Lindenfeld 2010). Hospitalizations due to ADHF exceed 1 million annually (Go 2013), and many of these patients will require care in an ICU setting. Appropriate pharmacologic management of patients in an ICU where ADHF is either a primary or a secondary

diagnosis is crucial to optimizing outcomes and assuring cost-effective care.

Prognostic Indicators

The Acute Decompensated Heart Failure National Registry initiative is aimed at improving risk stratification in patients admitted with ADHF. An analysis of data from over 65,000 ADHF admissions showed that in patients with an admission BUN of 43 mg/dL or greater, systolic blood pressure less than 115 mm Hg and SCr of 2.75 mg/dL or greater had a 21.9% risk of in-hospital mortality; this rate is 10–12 times greater than patients with none of these three factors (Fonarow 2005). Another analysis of 4031 patients found that advanced age, low systolic blood pressure, elevated respiratory rate, hyponatremia, and elevated BUN on hospital admission were all valid predictors of 30-day and 12-month mortality (Lee 2003). Understanding these presenting characteristics will assist the critical care pharmacist in tailoring medication interventions to the severity of illness and setting appropriate goals of care.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic pathophysiology of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction
- Knowledge of mechanism of action, pharmacokinetic, and pharmacodynamic properties of diuretics, vasodilators, and positive inotropic therapies
- Understanding of the clinical syndrome that leads to hospital admission because of acute decompensated heart failure (ADHF)
- Cardiac anatomy, including valve location and common types of valve dysfunction
- New York Heart Association functional classes of heart failure
- Forrester hemodynamic subsets of ADHF

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- [2013 ACCF/AHA Guideline for the Management of Heart Failure](#)
- Heart Failure Society of America. [2010 Comprehensive Heart Failure Practice Guideline](#)
- European Society of Cardiology. [Acute and Chronic Heart Failure: ESC Clinical Practice Guidelines](#)

Biomarkers/Laboratory Values

B-type natriuretic peptide (BNP) and its complementary enzymatic cleavage product, N-terminal pro B-type natriuretic peptide (NT-proBNP), are useful diagnostic discriminators in patients with an uncertain diagnosis of ADHF, given their clinical presentation alone. Secreted from the ventricles in response to acute volume overload, BNP and NT-proBNP are commonly elevated in patients with ventricular dysfunction. In a prospective, randomized trial of over 1500 patients presenting to emergency departments with an unclear cause of shortness of breath, an elevated BNP was a more accurate predictor of ADHF as the primary diagnosis than was a history of HF, presence of rales on examination, or paroxysmal nocturnal dyspnea (Maisel 2002). The degree of BNP elevation also correlated in a linear fashion with the severity of HF by New York Heart Association (NYHA) class. These results were subsequently reproduced using NT-proBNP as the diagnostic marker (Januzzi 2005), making either laboratory assay reasonable and reliable for the diagnosis of ADHF in a critical care setting. Since these trials, BNP or NT-proBNP has become a recommended component of the initial assessment of any patient with dyspnea that may be caused by ADHF (Yancy 2013; Lindenfeld 2010). However, several common ICU conditions such as renal failure, sepsis, significant burns, and severe pneumonia can also elevate BNP and NT-proBNP concentrations and impair this test's diagnostic accuracy (Yancy 2013). Moreover, plasma BNP concentrations increase, whereas NT-proBNP concentrations are reduced during chronic use of the combined angiotensin receptor neprilysin inhibitor sacubitril/valsartan (Packer 2015). B-type natriuretic peptide is a substrate of neprilysin-mediated breakdown, whereas NT-proBNP is not; thus, the BNP increase is a result of the effect of the medication, whereas NT-proBNP lowering is the result of clinical improvement.

Cardiac troponin can be used to determine the presence of myocardial cell death and predict outcomes in patients with ADHF. In a single-center study of 250 patients with ADHF admitted for heart transplant evaluation, cardiac troponin I was elevated in 49%, independent of HF etiology (ischemic vs. nonischemic). The troponin-positive cohort had worse initial invasive hemodynamic values, was more likely to have disease progression, and had twice the risk of death over the subsequent six months (Horwich 2003). Given these findings, current guidelines recommend cardiac troponin measurement at the time of ADHF admission for establishing prognosis and disease severity (Yancy 2013; Lindenfeld 2010).

Beyond these biomarkers, several more routine laboratory values may serve as valuable risk stratification tools. In patients admitted with ADHF, each 1-g/dL decrease in hemoglobin on admission has been associated with a 12% increase in the risk of death or rehospitalization at 60 days, a factor that maintained significance when controlled for markers of potential blood dilution caused by fluid overload (Felker 2003). Hyponatremia (defined as a serum sodium concentration

less than 135 mEq/L) is associated with increased rates of in-hospital and 60-day mortality in patients admitted with ADHF (Klein 2005). Therapeutic modalities to correct hyponatremia will be discussed later in this chapter.

HEMODYNAMICS

Hemodynamic monitoring of critically ill patients can be useful information for knowledgeable practitioners. Understanding normal cardiovascular parameters (Table 1-1) is crucial in the appropriate pharmacologic management of patients with cardiovascular abnormalities, particularly those refractory to fluid management. Patients in whom routine clinical assessment is insufficient may require a more comprehensive understanding of their hemodynamic condition using a variety of devices, ranging from older, more established devices to newer, less-validated models. These monitoring systems also vary in their invasiveness and consequently their risk profile.

Invasive Monitoring

The most invasive hemodynamic monitoring device available is the pulmonary artery catheter (PAC), commonly called a Swan-Ganz catheter (Swan 1970). This catheter can also measure, in a relatively continuous fashion, parameters that are not a feature of less-invasive monitoring techniques, such as pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic pressure/pulmonary artery diastolic pressure, CO/cardiac index (using thermodilution), and systemic vascular resistance (SVR). The PCWP is the premier measurement of “preload,” or the relative blood volume that will fill the left ventricle after passing through the lungs. Knowledge of whether the pulmonary artery pressures are significantly elevated can

determine the need for specialized treatment, such as pulmonary vasodilators or consideration for advanced therapies.

Another technique uses the Fick principle, whereby CO can be calculated by dividing the patient’s oxygen consumption (Vo_2 , measured in milliliters per minute) by the difference in arterial and venous oxygen saturation ($SaO_2 - Svo_2$) (Berton 2002). This measurement is usually obtained with a PAC because it requires the Svo_2 to be obtained from a sample of mixed blood in the pulmonary artery. Unfortunately, the CO value obtained by either thermodilution or Fick methods does not always correlate when measured simultaneously on the same patient. The CO values from a PAC can be difficult to interpret in the setting of significant tricuspid regurgitation or very low EF; the use of CO obtained using the Fick principle can be confounded by severe anemia, lung dysfunction, sepsis, and/or arteriovenous shunts. One published study of patients undergoing PAC placement in a catheterization laboratory showed a greater than 20% discrepancy in measured CO using these two methods in 43% of the patients studied (Fares 2012). When both methods are used in the same patient, many practitioners average the two values for clinical decision-making.

Risk of Invasive Monitoring

Although PAC data can be very useful in treating an individual patient with HF, PACs should not be used universally in a critical care setting. Despite early uptake in a broad ICU population, the SUPPORT trial tempered enthusiasm for PAC use after demonstrating significantly worse 30-, 60-, and 180-day survival rates in a propensity-matched analysis of ICU patients treated with PACs (Connors 1996). Patients with PACs also had higher cost of care and longer length of stay (LOS). The subsequent prospective, randomized ESCAPE trial of PAC use restricted to patients with ADHF was terminated because of concern for excess of adverse events such as infection, bleeding, catheter knotting, pulmonary artery damage, and ventricular arrhythmia in the absence of clinical benefit in the PAC arm (Binanay 2005). Of more concern, perhaps, is the potential for practitioners to misuse the information a PAC provides by titrating therapies to numeric hemodynamic goals without ensuring the patient’s clinical trajectory has improved. With these studies in mind, the decision to use PAC-guided therapy should be restricted to patient populations for which the benefit of invasive hemodynamic data acquisition has the greatest likelihood of exceeding the known risks.

Less-Invasive Monitoring

Hemodynamic monitoring can also be conducted in a manner that does not require placing a device in the cardiac chambers. A category of devices using transpulmonary indicator dilution incorporates principles similar to the aforementioned PAC, but with measurement devices in the peripheral vasculature. The PiCCO catheter requires a central venous

Table 1-1. Normal Hemodynamic Parameters

Parameter	Approximate Value
Pulmonary artery systolic pressure	25 mm Hg
Pulmonary artery diastolic pressure	10 mm Hg
Central venous pressure	0–4 mm Hg
Pulmonary capillary wedge pressure	8–12 mm Hg
Cardiac output	4–7 L/min
Cardiac index	2.8–3.6 L/min/m ²
Systemic vascular resistance	800–1200 dynes/s/cm ⁵

Information from: Hoffman EW. Basics of cardiovascular hemodynamic monitoring. *Drug Intell Clin Pharm* 1982;16: 657-64.

catheter for injecting cold saline and a femoral artery catheter to detect the temperature change as its method of transpulmonary thermodilution (Teboul 2016). The LiDCO uses the transpulmonary detection of lithium ion injected into the central venous catheter by a radial artery catheter. Both the PiCCO and the LiDCO allow for the continuous measurement of CO by tracking the magnitude of an arterial pressure waveform under the assumption that this waveform is the result of a predictable relationship between stroke volume and SVR. These peripheral devices also allow for measures of stroke volume responsiveness to fluid challenges; however, their reliability in assessing the benefits of volume removal in a patient with ADHF is less clear. Although both methods have been validated as accurate detectors of CO compared with PAC, they require recalibration when the patient's SVR is believed to have changed. Still less invasive is the trans-thoracic echocardiogram (TTE), which can detect ventricular over-dilation and assess adjacent vena cava dimensions in patients with fluid overload (Hollenberg 2013). The echocardiogram is limited because it can only provide "snapshots" of hemodynamic parameters, which may not be ideal for the dynamic treatment of the critically ill patient with markedly diminished CO in the setting of ADHF.

Applications of Hemodynamic Monitoring

An appropriate plan for how using the specific data derived from a cardiac monitoring device will improve the patient's clinical outcomes should be determined before initiating monitoring. An expert panel of the European Society of Intensive Care Medicine identified several key reasons for choosing to assess cardiac function in various shock states, including if the cause of the shock is unknown or cannot be determined from integrating a clinical examination, assessment of laboratory values, and clinical context of the presentation. Moreover, the panel acknowledged that understanding of cardiac function and fluid status can aid in selecting the next intervention and then in evaluating its efficacy (Cecconi 2014).

The TTE can provide information about cardiac anatomy and function and can quickly be applied in almost all critical care settings. As such, it is an excellent first-line tool for assessing acute pump dysfunction and/or valvular problems that may be impairing the efficacy of fluid-lowering therapies such as diuretics. Although the TTE provides relatively static assessment, it can be repeated at reasonable intervals to assess response to therapies during a hospital admission. If the TTE does not provide enough "real-time" data, transpulmonary thermodilution such as PiCCO and LiDCO can provide a reliable assessment of cardiac stroke volume and volume status in a continuous fashion, making it more useful in patients with dynamic cardiac conditions. Ultimately, PAC placement should be considered when there is concern for advanced cardiac dysfunction, the potential for superimposed clinical scenarios (i.e., ADHF and concomitant

pulmonary embolism), and/or when patients do not respond as expected to empiric ADHF therapies.

The Heart Failure Society of America (HFSA) guidelines on the management of ADHF clearly state that routine use of PAC for invasive monitoring in patients with ADHF is not appropriate (Lindenfeld 2010). However, PAC may be appropriate in worsening renal function (WRF) and/or failure to meet urinary output (UOP) goals with aggressive multidrug diuresis, hypotension with concern for worsening CO that may progress to cardiogenic shock, uncertain intracardiac volume status when estimations of central venous pressure (CVP) by central line are insufficient, and ADHF with known (or suggested) clinically significant pulmonary hypertension and/or concern for right ventricular dysfunction. It is also reasonable to initiate PAC in patients who may require inotropic therapy (Cecconi 2014; Lindenfeld 2010). In any of these cases, the PAC information needs to be interpreted by practitioners with expertise in PAC-guided management, and the PAC should be removed as soon as the data it provides are no longer driving decision-making.

DIURETIC THERAPIES

Use of diuretic therapies is considered a mainstay of therapy for managing volume overload in ADHF, despite limited data to support and guide their use. Dose escalation, alternative drug delivery, combination diuretic therapy, and add-on therapies are different strategies that may be considered to optimize diuresis. Patients presenting in HF subset II or IV should be considered for diuretic therapy with the goal of optimizing symptoms by relieving dyspnea and improving volume status. Both the HFSA and the American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines recommend that patients with signs of volume overload be treated with intravenous loop diuretics at doses equaling or exceeding a patient's home dose, when applicable (Yancy 2013; Lindenfeld 2010). Monitoring response to therapy includes assessing signs and symptoms of volume overload including resolution of dyspnea and resolution of edema such as improvement in jugular venous distension. Changes in body weight and measurements of fluid intake and output are recommended to assess the patient's response. When response to diuretic therapies is considered inadequate, the ACC/AHA and HFSA guidelines recommend advancing doses, or adding a second diuretic agent to enhance response (ACC/AHA 2013, HFSA 2010).

Loop Diuretics

The appropriate dosing and delivery strategy for intravenous loop diuretics has been an ongoing debate in ADHF treatment. The onset of action for intravenous loop diuretics is minutes, creating a short period from dose administration to diuretic effect (Table 1-2). Given the relatively short half-lives of the available intravenous loop diuretics, most patients will require several daily doses to maintain a diuretic effect.

Table 1-2. Loop Diuretic Comparison

	Furosemide	Bumetanide	Torsemide	Ethacrynic Acid
Bioavailability	22%–70%	80%–100%	70%–100%	100%
Half-life	1½–3 hr	1–1½ hr	3–7 hr	1–4 hr
Onset of action (IV)	5 min	2–3 min	10 min	5 min
Oral equivalent dose	40 mg	1 mg	20 mg	50 mg
Oral to IV conversion	2:1	1:1	1:1	1:1

IV = intravenous(ly).

Information from: Knauf H, Mutschler H. Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clin Pharmacokinet* 1998;34:1-24; Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail* 2010;16:e1-194; and Wargo K, Banta W. A comprehensive review of the loop diuretics: should furosemide be first line? *Ann Pharmacother* 2009;43:1836-47.

Escalating doses are often needed to achieve an adequate response. The dissipation of effect between doses and the risk of hypotension with high-dose IVB has led to the use of CIV loop diuretics in an effort to avoid diuretic-free periods and minimize adverse effects with high IVB doses. Both delivery methods may cause hypokalemia and hypomagnesemia; therefore, it is important to monitor and replace electrolytes as needed (Wargo 2009). Most available literature evaluating loop diuretics in ADHF has been limited to the use of furosemide or a conversion to furosemide equivalents. Although there is debate about the best approach for conversion between loop diuretics, the data discussed in this chapter use a conversion to oral furosemide equivalents, with a subsequent conversion to equivalent intravenous doses (Shulenberg 2016; Felker 2011; Wargo 2009). Ethacrynic acid is an effective alternative for patients with true and severe sulfa allergies. However, it has a higher risk of ototoxicity (Molnar 2009).

Older studies are relatively small and have had conflicting results when comparing CIV with IVB diuretics in ADHF. The Diuretic Optimization Strategies Evaluation (DOSE) trial was expected to clarify which approach to dosing and administration of loop diuretics would be most favorable. The DOSE trial compared CIV and IVB dosing every 12 hours using both high-dose (2.5 times the oral home diuretic dose given intravenously) and low-dose (equivalent oral home diuretic dose equivalent given intravenously) dosing strategies. Patients receiving a home diuretic equivalent of 80–240 mg/day of oral furosemide were enrolled within 24 hours of presentation and were excluded from the study if intravenous vasodilator or intravenous inotrope administration was required. Patients received the concealed study treatment for 72 hours, with the ability for the managing physician to increase the total diuretic dose by 50%, continue current treatment, or discontinue intravenous diuretics at 48 hours. The primary efficacy

end point evaluated the patient's global assessment of symptoms using a visual analog scale from baseline to 72 hours. The primary safety outcome was the change in SCr from baseline to 72 hours. There was no difference between CIV and IVB or between low-dose versus high-dose groups for the co-primary end point. Significant differences occurred in the secondary end points of change in weight and net fluid loss in favor of the high-dose strategy. The high-dose group had a significant increase in the incidence of SCr rise by more than 0.3 mg/dL compared with the low-dose group, but this did not correlate with worsening clinical outcomes at 60 days.

Although the DOSE trial is the largest study to date investigating dosing strategies of loop diuretics in ADHF, it found no significant difference in the primary outcome of patient symptom assessment or a change in SCr at 72 hours (Table 1-3). An increased incidence of dose escalation occurred in the low-dose group, implying that the low-dose strategy was inadequate for achieving treatment goals. Greater weight loss and net fluid loss using the high-dose strategy suggest that a 2.5-fold increase in dose from home diuretics results in a greater loss of volume leading to a greater weight reduction, regardless of the administration strategy (Felker 2011). Importantly, the DOSE trial did not take diuretic bioavailability into account, rather simply conducted a direct conversion and administered an intravenous dose that was a 2.5-fold increase in the oral dose (e.g., furosemide 40 mg PO twice daily converted to furosemide 100 mg IV twice daily).

After publication of the DOSE trial, a meta-analysis was published comparing CIV with IVB loop diuretic use in ADHF, which included 10 trials that met the investigators' search criteria. The analysis found no difference in UOP between groups, even when significant heterogeneity across studies was accounted for on the basis of varied time intervals for UOP collection. Only 3 of the 10 studies reported on weight loss. The weighted mean difference was in favor of CIV over

Table 1-3. DOSE Trial Study End Points (Baseline to 72-Hr Assessment)

End Point	CIV (n=152) vs. IVB (n=156)	Low Dose (n=151) vs. High Dose (n=157)
Patient-reported global assessment of symptoms, mean AUC	4373 ± 1404 vs. 4236 ± 1440, p=0.47	4171 ± 1436 vs. 4430 ± 1401, p=0.06
Change in SCr (mg/dL)	0.07 ± 0.03 vs. 0.05 ± 0.3, p=0.45	0.04 ± 0.3 vs. 0.08 ± 0.3, p=0.21
AUC for dyspnea	4699 ± 1573 vs. 4456 ± 1468, p=0.36	4478 ± 1550 vs. 4668 ± 1496, p=0.04
Increase in SCr > 0.3 mg/dL	19% vs. 17%, p=0.64	14% vs. 23%, p=0.04
Change in weight (kg)	-8.1 ± 10.3 vs. -6.8 ± 7.8, p=0.2	-6.1 ± 9.5 vs. -8.7 ± 8.5, p=0.01
Net fluid loss (mL)	4249 ± 3104 vs. 4237 ± 3208, p=0.89	3575 ± 2635 vs. 4899 ± 3479, p=0.001

AUC = area under the curve; CIV = continuous intravenous infusion; IVB = intravenous bolus; LOS = length of stay.

Information from: Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797-805.

IVB (0.78; 95% CI, 0.03–1.54), and no heterogeneity was found. The incidence of hypokalemia was assessed in 6 of the 10 studies with no difference between groups. There was also no consistent benefit with CIV over IVB for changes in UOP or effect on serum electrolytes across studies. The results of this meta-analysis is consistent with more recently published clinical trials, suggesting no benefit in effects on renal function with CIV compared with IVB loop diuretics (Wu 2014).

Clinical trials comparing CIV with IVB loop diuretics have not evaluated the same clinical outcomes. Therefore, comparisons of one trial with another are challenging, and it is difficult to establish consistent trends or replicate results. Although strategies suggested to optimize response to diuresis may include increasing the loop diuretic dose, data analyses have suggested that increasing diuretic doses is associated with WRF and mortality (Hasselblad 2007; Butler 2004). And thus, other approaches are often implemented to overcome loop diuretic resistance.

Thiazide Diuretics

Loop diuretic resistance often complicates ADHF management. Among the many proposed mechanisms for diuretic resistance is increased sodium reabsorption in the distal nephron. As loop diuretics inhibit the retention of sodium at the loop of Henle, the distal segment of the nephron is exposed to an increased sodium load that may lead to a rebound in sodium reabsorption. The distal nephron may also develop a compensatory hyperactivity as a result of long-term diuretic use, further increasing sodium reabsorption. In addition, a post-diuretic effect may lead to sodium reabsorption. As the effect of each dose of loop diuretic subsides, the nephron increases sodium reabsorption because there is no longer active antagonism at the site (Jentzer 2010; Ellison 1991). Finally, there is the concept of “diuretic braking,” which suggests that with each additional dose of diuretic and

sustained therapy, response to the diuretic declines (Felker 2009; Loon 1989).

In an effort to overcome diuretic resistance, adding a thiazide diuretic produces a synergistic effect with loop diuretics through its blockade of sodium reabsorption at the distal tubule. Combination diuretic therapy has long been used, despite limited published data. As of 2010, published literature studying combination diuretic therapy in ADHF included 300 patients. The agents studied include metolazone, hydrochlorothiazide, oral chlorothiazide, quinethazone, and bendroflumethiazide (Jentzer 2010). Combination diuretic therapy data analyses have focused on using intravenous loop diuretics with oral thiazide or thiazide-like diuretics, although variable oral absorption and poor bioavailability complicate the use of oral therapies in ADHF. Medications such as oral hydrochlorothiazide and intravenous chlorothiazide may lose efficacy at an estimated creatinine clearance (eCrCl) less than 30 mL/minute/1.73 m², whereas oral metolazone may be more effective in patients with significant renal impairment. The HFSA guidelines recommend adding oral metolazone, spironolactone, or intravenous chlorothiazide to overcome diuretic resistance; however, the strength of evidence of this recommendation is limited to expert opinion.

In a retrospective review evaluating the use of intravenous chlorothiazide in ADHF, intravenous chlorothiazide was compared with oral metolazone in patients with refractory diuresis. Over the 72-hour period, patients in the intravenous chlorothiazide group received more intravenous furosemide than did patients in the metolazone group (p<0.001). The median daily dose of metolazone was 2.5 mg/day. The median intravenous chlorothiazide dose advanced with each day of therapy (day 1: 500 mg, day 2: 750 mg, day 3: 1000 mg). The primary outcome, net UOP at 72 hours, was greater with metolazone, but the difference was not statistically significant. Hypokalemia occurred in almost half of the patients but did not differ between groups.

Although there was no significant difference between groups in net UOP after 72 hours of therapy, the authors commented on differences between groups suggesting that metolazone is more favorable. The chlorothiazide group received a higher cumulative dose of intravenous furosemide that was twice that administered in the metolazone group. The chlorothiazide group also received more frequent dose escalation between days 1 and 3 of therapy, and the median LOS was longer in the chlorothiazide arm at 16 days than at 7 days. The authors concluded that the patients receiving intravenous chlorothiazide were treated more aggressively with diuretic therapy, and the longer LOS may have reflected higher acuity of these patients. The numerically greater net UOP in the trial with metolazone suggests that metolazone is as good as intravenous chlorothiazide in this patient population (Moranville 2015).

Another retrospective assessment assessed the noninferiority of metolazone to intravenous chlorothiazide when added to intravenous loop diuretic therapy. The primary end point of change in 24-hour net UOP after administration of thiazide add-on therapy did not differ between groups ($p=0.308$) and met the prespecified criteria for noninferiority with 80% power. The average dose of metolazone was 5.8 mg (± 3.5 mg),

with a mean intravenous chlorothiazide dose of 491 mg (± 282 mg). Patients in the intravenous chlorothiazide arm received higher loop diuretic doses ($p=0.004$) and were more likely to receive intravenous loop diuretics as a CIV ($p=0.001$). When the noninferiority analysis controlled for ICU admission, NYHA class, baseline SCr, intravenous loop diuretic dose, IVB versus CIV loop diuretic, and net UOP before thiazide addition, there remained no difference between groups. Hypokalemia occurred more often with intravenous chlorothiazide, but severe hypokalemia did not differ between groups (Table 1-4). The ability of oral metolazone to meet the noninferiority threshold suggests that oral metolazone is a reasonable first-line approach to add-on thiazide diuretic therapies (Shulenberg 2016).

The previously discussed studies have evaluated oral thiazide therapy compared with intravenous therapy, whereas a 2016 study evaluated adding intravenous chlorothiazide to the therapy of patients who were unresponsive to oral metolazone. The study identified 45 patients who received intravenous loop diuretics and metolazone of at least 5 mg and a subsequent dose of intravenous chlorothiazide of at least 500 mg. The primary end point of net-negative UOP of 500 mL or more during the 12 hours after administration of

Table 1-4. Summary of Studies Evaluating Thiazide Diuretics in ADHF

Study	Study Design	Primary End Points	Secondary End Points
Moranville et al	Retrospective chart review: <ul style="list-style-type: none"> ADHF with eCrCl 15–50 mL/min/1.73 m² IV furosemide monotherapy ≥ 72 hr of thiazide exposure CTZ (n=22) or MTZ (n=33) 	Median net UOP at 72 hr was greater with MTZ than with CTZ but was not significantly different (4828 mL vs. 3779 mL, $p=0.16$)	Hypokalemia did not differ between groups LOS was significantly shorter in the MTZ group than in the CTZ group (7 days vs. 16 days, $p=0.03$)
Shulenberg et al	Retrospective cohort study: <ul style="list-style-type: none"> IV furosemide ≥ 160 mg/day CTZ (n=88) or MTZ use (n=89) Noninferiority design, 80% power Baseline renal function (CTZ 1.8 ± 0.9 vs. MTZ 1.9 ± 1.2, $p=0.748$) 	MTZ met threshold for noninferiority in net UOP (lower bound of 95% CI < 500 mL net UOP, MTZ 1319.6 ± 1517.4 vs. CTZ 1397.6 ± 1370.7 mL, lower bound 95% CI = 437.4 mL, $p=0.026$)	Hypokalemia (serum potassium < 4.0 mEq/L) occurred more often with CTZ than with MTZ (75% vs. 60.7%, $p=0.045$) Severe hypokalemia (serum potassium < 3.5 mEq/L) was no different between therapies (30.7% vs. 24.7%, $p=0.443$)
Cardinale et al	Retrospective cohort study: <ul style="list-style-type: none"> ADHF using IV loop diuretic Administration of MTZ ≥ 5 mg followed by CTZ ≥ 500 mg (n=45) 	Net-negative UOP ≥ 500 mL 12 hr after thiazide-type diuretic dose occurred similarly using MTZ vs. CTZ (35.5% vs. 42.2%, $p=0.581$)	Median 12-hr UOP greater with CTZ than with MTZ (1075 mL vs. 810 mL, $p=0.363$) Hypokalemia and hypomagnesemia did not differ between groups (MTZ 22.2% vs. CTZ 26.7%, $p=0.688$)

ADHF = acute decompensated heart failure; CTZ = IV chlorothiazide; IQR = interquartile range; MTZ = oral metolazone.

Information from Cardinale M, Altschuler J, Testani JM. Efficacy of intravenous chlorothiazide for refractory acute decompensated heart failure unresponsive to adjunct metolazone. *Pharmacotherapy* 2016;36:843-51; Moranville MP, Choi S, Hogg J, et al. Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance. *Cardiovasc Ther* 2015;33:42-9; and Shulenberg CE, Jiang A, Devabhakthuni S, et al. Efficacy and safety of intravenous chlorothiazide versus oral metolazone in patients with acute decompensated heart failure and loop diuretic resistance. *Pharmacotherapy* 2016;36:852-60.

the add-on therapy occurred more often after intravenous chlorothiazide use but was not significantly different from net UOP with continued oral metolazone. This study evaluated patients with a high severity of illness, as reflected by a baseline eCrCl of 27.4 mL/minute/1.73 m² (\pm 19.4 mL/minute/1.73 m²), average intravenous furosemide dose of 400 mg/day, average LOS of 34.7 days, and in-hospital mortality rate of 35.6%. Although the study evaluated only a short period for diuretic effect monitoring, the results suggest that intravenous chlorothiazide has no significant advantage over oral metolazone in severely ill patients with refractory diuresis (Cardinale 2016).

Albumin as a Predictor of Diuretic Response

Patients with ADHF requiring diuresis are at risk of WRF. Given that baseline characteristics and management strategies may both play a role in the risk of WRF, investigators have evaluated which characteristics may place a patient at higher risk of WRF in ADHF. A retrospective analysis of 177 patients treated with CIV loop diuretics determined the characteristics associated with increased the risk of WRF, as defined by an increase in SCr by 0.3 mg/dL or more. In this analysis, only a serum albumin of 3 g/dL or less was associated with WRF (HR 2.87; 95% CI, 1.60–5.15; $p=0.0004$) and an increase in in-hospital mortality (OR 2.86; 95% CI, 1.24–6.65; $p=0.011$) (Clarke 2013). Another study assessed data from the DOSE and ROSE AHF (Renal Optimization Strategies Evaluation) trials to evaluate the relationship between serum albumin and the outcomes of WRF, worsening HF, and clinical decongestion at 72 hours. The ROSE AHF trial was designed to prospectively assess the use of renal dose dopamine or low-dose nesiritide as adjunctive therapy for ADHF as compared to placebo (outcomes to be discussed in the Dopamine and Vasodilator Therapies sections that follow). Baseline serum albumin concentrations were obtained and included for 456 patients from the two prospective studies. The mean baseline albumin was 3.5 g/dL (\pm 0.5 g/dL). Lower albumin concentrations were associated with greater rates of rales and increased peripheral edema, but not with WRF, worsening HF, or freedom from congestion. These results contradict the findings of the first analysis, suggesting that, at this time, baseline serum albumin cannot be used as a predictor of response or adverse event risk to diuretic therapies (Grodin 2016).

Hypertonic Saline

Adverse effects and resistance to diuretic therapies may be exacerbated by rapid intravascular volume depletion that can occur with aggressive diuresis. The weakened effect of repeated loop diuretic doses, or the “braking effect,” may be caused by reduced intravascular volume delivery despite an excess of extracellular fluid. Concomitant administration of hypertonic saline solution in addition to diuretics has been proposed as a strategy to overcome these effects. By providing a rapid osmotic effect, the movement of extracellular free

water into the intravascular space is then available for excretion using diuretic therapies (De Vecchis 2015). Literature investigating use of hypertonic saline solution for ADHF management have used varied doses and evaluated different outcomes, and studies have also ranged in size.

The largest trial to date of hypertonic saline solution in ADHF enrolled 1927 patients with NYHA class III HF and left ventricular EF less than 40%. All patients were treated with furosemide 250 mg IVB twice daily, with the hypertonic saline solution group receiving hypertonic saline solution intravenously twice daily (150 mL of 1.4%–4.6% sodium chloride). The hypertonic saline solution concentration was determined on the basis of serum sodium. Patients with a serum sodium less than 125 mEq/L received the most concentrated solution, and those with a serum sodium greater than 135 mEq/L received the most dilute. The study more aggressively restricted dietary sodium intake in the control arm than in the hypertonic saline solution intervention arm (hypertonic saline solution 120 mmol/day, 2.75 g/day; control: 80 mmol/day, 1.84 g/day) and continued this oral sodium restriction strategy for the duration of follow-up (31–83 months, mean 57 months). The primary end points were LOS, hospital readmission, and mortality. Patients treated with hypertonic saline solution had a significantly reduced LOS (3.5 days vs. 5.5 days, $p<0.0001$), a greater eCrCl at discharge (55.4 mL/minute/1.73 m² vs. 48.7 mL/minute/1.73 m², $p<0.0001$), and an increase in daily diuresis ($p<0.0001$). In addition, hypertonic saline solution use was associated with a shorter LOS and reduced mortality and hospitalization at 57-month follow-up. The long-term effect of hypertonic saline, as measured by hospitalizations and mortality, should be interpreted cautiously given a concomitant outpatient sodium restriction intervention likely influenced this endpoint (Paterna 2011).

A smaller placebo-controlled trial assessed the effects of hypertonic saline solution on renal function in ADHF. The primary end point was an increase in SCr of 0.3 mg/dL or more. Patients received loop diuretics, dose adjusted to achieve a weight loss of 0.5–1 kg per day. Within the 72-hour protocol, the hypertonic saline solution group received 100 mL of hypertonic saline solution 7.5% over 1 hour twice daily, whereas the placebo arm received sodium chloride 0.9% 100 mL infused over 1 hour twice daily. After 32 patients had received study treatment, the trial was terminated. There was a 70% difference in the primary endpoint between the hypertonic saline solution arm and the placebo arm (10% vs. 50%, $p=0.01$), with the peak SCr at 72 hours after the intervention. There was no significant difference in SCr between the two groups at 2 weeks and 30 days after the intervention. Patients in the hypertonic saline solution group required lower furosemide doses to achieve the targeted weight-loss goal (120 mg vs. 160 mg, $p<0.001$). Although the study was small, it suggests that hypertonic saline solution plays a role in renoprotective effects during active diuresis in ADHF (Issa 2013).

In a meta-analysis of 10 trials that treated patients with ADHF with loop diuretics and hypertonic saline solution, the outcomes measured within the index admission of hypertonic saline solution intervention included LOS, weight loss, and renal function. Length of stay was evaluated in seven trials and was 3.13 days shorter using hypertonic saline solution ($p < 0.00001$). Weight loss was assessed in eight trials and increased by an average of 2 kg ($p = 0.0002$). In eight trials assessing renal function, patients treated with hypertonic saline solution had a weighted mean decrease in SCr by 0.2 mg/dL, whereas those treated with loop diuretics had only a weighted mean increase of 0.3 mg/dL ($p < 0.00001$). The benefits in LOS, weight loss, and renal function remained similar with the removal of each individual trial in a sensitivity analysis (Gandhi 2014).

While these studies suggest that hypertonic saline solution is well tolerated in this population, the long-term benefits of using hypertonic saline solution to augment diuresis in ADHF will need to continue to be studied. Use of this therapy is not addressed in current HF guidelines (ACC/AHA 2013, HFSA 2010).

DOPAMINE

Although the use of diuretics is often effective for volume management, potential adverse effects on renal function remain a concern. As previously discussed, augmentation strategies are also often required in diuretic resistance. Using dopamine in addition to loop diuretics is one potential strategy to overcome diuretic resistance, with a proposed benefit in also providing renal protection. Data in patients without ADHF have suggested benefits in UOP and SCr with low-dose dopamine added to diuretics in the first 24 hours of therapy; however, sustained benefit throughout treatment has not been shown (Fredrich 2005).

The Dopamine in the Acute Decompensated Heart Failure (DAD-HF) trials evaluated adding a dopamine infusion to CIV furosemide. The DAD-HF I trial randomized 60 patients with ADHF to high-dose CIV furosemide (20 mg/hour) or low-dose CIV furosemide (5 mg/hour) plus dopamine (5 mcg/kg/minute) for 8 hours. The study evaluated WRF at 24 hours from randomization, defined as an increase in SCr greater than 0.3 mg/dL. The effect on UOP was similar between the two groups, and both groups had an improvement in dyspnea scores ($p = 0.575$). Worsening renal function at 24 hours occurred more often in the high-dose furosemide group than in the low-dose furosemide plus dopamine arm (30% vs. 6.7%, $p = 0.042$). When the change in SCr was assessed throughout the hospitalization, there was no significant difference between the groups ($p = 0.256$). The DAD-HF I trial suggests that adding dopamine 5 mcg/kg/minute to a low-dose CIV of furosemide is an equally effective strategy for diuresis with less risk of renal harm (Giamouzis 2010).

In DAD-HF I, dopamine was administered at 5 mcg/kg/minute, a dose known to target not only the dopaminergic

receptors, but also β receptors. Therefore, it cannot be distinguished whether the reduction in WRF was the result of renoprotective effects or inotropic effects of dopamine. The appropriateness of an inotrope in patients should be considered when applying the dosing strategy used in DAD-HF I. In addition, the study used two doses of CIV furosemide and paired the dopamine infusion with the low-dose diuretic infusion. Therefore, it is difficult to determine whether the lower incidence of WRF was the result of adding dopamine or the reducing the diuretic dose. Finally, the infusion duration of 8 hours makes it difficult to determine what benefit or risk might occur with a more prolonged infusion of dopamine.

To address one of these limitations, the DAD-HF II trial replicated the DAD-HF I trial with the addition of a low-dose CIV furosemide arm. The DAD-HF II trial enrolled 161 patients into three arms: high-dose CIV furosemide (20 mg/hour), low-dose CIV furosemide (5 mg/hour) with dopamine (5 mcg/kg/minute), and low-dose CIV furosemide alone (5 mg/hour) for 8 hours. The primary outcomes were 60-day and 1-year all-cause mortality and HF hospitalizations. The study was designed to enroll 450 patients in order to achieve 80% power, but the trial was terminated early after enrolling 161 patients because of the significant increase in heart rate in the dopamine arm. The baseline heart rate was no different between the groups, and the increase in heart rate was not explained by a history of atrial fibrillation.

Evaluation of the 161 patients enrolled in DAD-HF II revealed no difference between the three groups in UOP or weight loss at 24 hours. The primary outcomes of all-cause mortality and HF hospitalizations were no different at 60 days or 1 year. There was a significant increase in WRF in the high-dose furosemide arm from baseline to 24 hours, but the three groups did not differ in peak SCr. It was concluded that the high-dose furosemide strategy results in an early decline in renal function but that this difference is not sustained over time. The DAD-HF II trial concluded that dopamine 5 mcg/kg/minute may be associated with greater adverse effects and no benefit (Triposkiadis 2014).

To compare lower doses of dopamine with placebo, the Renal Optimization Strategies Evaluation (ROSE AHF) trial was performed (Table 1-5). In addition, the ROSE trial was designed to assess the use of low-dose dopamine as well as low-dose nesiritide as adjunctive therapies for ADHF (outcomes discussed in the section on vasodilator therapies). The ROSE AHF trial randomized 360 patients with ADHF and an eCrCl of 15–60 mL/minute/1.73 m² to dopamine 2 mcg/kg/minute, nesiritide 0.005 mcg/kg/minute, or placebo for 72 hours. Patients were treated with intravenous loop diuretics with a recommendation to dose intravenous diuretics at 2.5 times the total daily outpatient dose of furosemide. For the first 24 hours, doses were administered IVB every 12 hours. Co-primary end points for the trial were 72-hour cumulative UOP to assess decongestion and change in serum cystatin

Table 1-5. ROSE Trial Outcomes

	Placebo (n=119)	Dopamine (n=122) ^a	Nesiritide (n=119) ^a
Cumulative urine volume at 72 hr, mL	8296 (7762–8830)	8524 (7917–9131), p=0.59	8574 (8014–9134), p=0.49
Change in cystatin C concentration at 72 hr, mg/L	0.11 (0.06–0.16)	0.12 (0.06–0.18), p=0.72	0.07 (0.01–0.13), p=0.36
Change in weight at 72 hr, lb	-7.73 (-9.01 to -6.44)	-7.40 (-8.83 to -5.98), p=0.82	-7.15 (-8.57 to -5.73), p=0.67
Change in Cr at 72 hr, mg/dL	0.02 (-0.4 to 0.08)	0 (-0.7 - 0.08), p=0.78	0.02 (-0.06 to 0.09), p=0.90
Dyspnea visual analog scale, AUC at 72 hr	4998 (4723–5272)	4936 (4660–5211), p=0.92	4831 (4592–5070), p=0.89
Study drug stopped or dose decreased because of hypotension	12/115 (10.4%)	1/111 (0.9%), p<0.001	22/117 (18.8%), p=0.07
Study drug stopped or dose reduced because of tachycardia	1/115 (0.9%)	8/111 (7.2%), p<0.001	0/117 (0%), p=0.50
Days alive and free from HF hospitalizations at 60 days	46.6 (44.0–49.2)	47.3 (45.0–49.6), p=0.68	47.3 (44.9–49.7), p=0.67

^aThe p value reflects placebo vs. drug identified in corresponding column.

Information from: Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013;310:2533-43.

C, a marker of renal function, at 72 hours from enrollment to assess renal function. There was no difference in cumulative UOP at 72 hours with the addition of low-dose dopamine, nor was there significant change in cystatin C concentrations, suggesting there was no renal-protective effect with the addition of low-dose dopamine. More patients required study drug discontinuation or dose reduction in the placebo arm than in the dopamine arm, but the overall discontinuation rates were no different between the groups. The ROSE trial suggests that adding low-dose dopamine to loop diuretics does not benefit patients with ADHF with moderate renal dysfunction (Chen 2013).

According to the 2013 ACC/AHA HF guidelines, low-dose dopamine may be considered to improve diuresis and preserve renal function and renal blood flow, class IIb and level of evidence B recommendation. However, this recommendation was made after the publication of DAD-HF I but before the DAD-HF II and ROSE AHF studies had been published.

VASODILATOR THERAPIES

Vasodilator therapies are often added to diuretics for ADHF management because of their ability to reduce PCWP and SVR, optimize CO, and improve dyspnea. To date, however, no intravenous vasodilator has been shown to modify mortality outcomes in a prospective trial. The 2013 ACC/AHA guidelines suggest that intravenous nitroglycerin, nitroprusside, or nesiritide can be considered together with diuretics

in patients without symptomatic hypotension for the relief of dyspnea. Likewise, the 2010 HFSA ADHF guidelines suggest that intravenous vasodilators can be used for rapid improvement in congestive symptoms. More specifically, the HFSA guidelines suggest nitroglycerin or nitroprusside in the setting of acute pulmonary edema or severe hypertension because of their ability to rapidly produce venous dilatation, resulting in a reduction in preload. Use of intravenous vasodilators may require additional intravenous access and increased monitoring of hemodynamics and may raise concerns about adverse effects such as hypotension, cyanide toxicity, headache, and renal dysfunction. While initiation of these agents may begin in acute situations when needed for acute pulmonary edema or severe hypertension, patients should be transferred to an ICU for more intensive monitoring if therapy is to be continued. Although these medications are used to optimize hemodynamics, there have been reports that their use may be associated with neurohormonal activation (Elkayam 2008).

Intravenous nitroglycerin has predominant venous dilation effects, reducing preload. Titrating doses to achieve a desired decrease in CVP, PCWP, or arterial dilation is often limited by adverse effects such as headache and tachyphylaxis (Elkayam 2004). Sodium nitroprusside is a rapid-acting and potent venous and arterial vasodilator. Because of its risk of hypotension, it is typically administered in an ICU setting and is often monitored with a PAC or an arterial line for accurate assessment of mean arterial blood pressure. Concerns

surrounding the use of nitroprusside usually involve the risk of thiocyanate toxicity, though the incidence in HF is rare (Elkayam 2008).

The largest evaluation of nitroprusside in ADHF was a retrospective evaluation of 175 NYHA class III or IV patients treated with nitroprusside or placebo for ADHF with a cardiac index of 2 L/minute/m² or less. Patients were treated with a PAC during the evaluation, and nitroprusside therapy was titrated to a mean arterial pressure (MAP) of 65–70 mm Hg, according to institution protocol. Patients treated with nitroprusside had a higher CVP ($p<0.001$), PCWP ($p<0.001$), MAP ($p=0.01$), and SVR ($p=0.002$) at baseline than did patients receiving placebo. At the time of PAC removal, the MAP and pulmonary pressures were no different between groups, but the cardiac index was increased with nitroprusside (placebo 2.4 ± 0.5 vs. nitroprusside 2.6 ± 0.5 , $p<0.016$). Significantly more patients received hydralazine and/or isosorbide dinitrate at discharge in the nitroprusside arm. This is likely because the institution protocol allowed for transition from intravenous to oral vasodilators to promote the weaning of nitroprusside. Patients were followed for a median of 25.7 months from the time of PAC placement. Analysis for all-cause mortality (OR 0.48, $p=0.005$) and all-cause mortality or cardiac transplantation (OR 0.64, $p=0.016$) was significantly lower for patients treated with nitroprusside. In a univariate model, use of oral vasodilators was not associated with the same improvement in outcomes, but a transition from nitroprusside to vasodilators was associated with a reduction in all-cause mortality ($p=0.03$). This retrospective analysis is the largest study to date on the use of nitroprusside for ADHF management. These outcomes suggest that patients with increased filling pressures and reduced cardiac index with adequate MAP and SVR will benefit from nitroprusside use when treated according to dose titration, with conversion to oral vasodilators (Mullens 2008).

Nesiritide is recombinant human brain natriuretic peptide that matches the hormone produced by the left ventricle under increased filling pressures and wall stress. It is a rapid-acting and potent venous and arterial dilator that can reduce preload and afterload and increase CO (Elkayam 2004). In the VMAC trial, nesiritide compared with nitroglycerin and placebo had positive effects on PCWP measurements and patient self-evaluation of dyspnea with short-term (24 hours or less) use (VMAC 2002). After the VMAC trial and the FDA approval of nesiritide, retrospective analyses suggested an association between nesiritide and an increased risk of death or renal impairment. This made the role of nesiritide in managing ADHF unclear (Sackner-Bernstein 2005a; Sackner-Bernstein 2005b).

In an effort to clarify the role of nesiritide, the ASCEND-HF trial compared nesiritide with placebo for 24–168 hours of therapy at the standard dosing strategy of a 2-mcg/kg bolus, followed by a 0.01-mcg/kg/minute infusion. The ASCEND-HF study showed no benefit in symptom improvement or

outcomes with nesiritide. Given the increased risk of hypotension, cost of medication, and nonsignificant change in rehospitalizations for HF or death, the ASCEND-HF trial suggests no place for the routine use of nesiritide (O'Connor 2011).

Small retrospective studies have suggested that a lower nesiritide dose without an initial bolus has beneficial effects on renal function in ADHF (Riter 2006). The ROSE AHF trial included a low-dose nesiritide arm dosed at 0.005 mcg/kg/minute without a bolus. No difference occurred with low-dose nesiritide compared with placebo in urine volume or change in cystatin C concentrations at 72 hours (see Table 1-5). A significant increase in treatment failure at 72 hours with nesiritide was reported in 48 patients ($p=0.04$). This composite outcome included significant hypotension as well as worsening HF and type 1 cardiorenal syndrome, which was probably driven by the increased rate of hypotension with low-dose nesiritide. Given the lack of benefit in UOP and preservation of renal function, use of low-dose nesiritide does not modify the outcomes of patients with ADHF (Chen 2013).

Vasodilator therapy in ADHF focuses on medications with a strong venous dilatory effect in order to treat pulmonary congestion. Intravenous calcium channel blockers are arterial vasodilators and are not currently recommended by HF guidelines. Patients with ADHF may present in a hypertensive state, in which the acute state of hypertension causes fluid redistribution leading to pulmonary congestion. The PRONTO trial evaluated the use of clevidipine for blood pressure control in ADHF compared with standard of care. All patients were admitted with ADHF, systolic blood pressure of 160 mm Hg or greater, and dyspnea score of 50 or greater on a 100-mm visual analog scale. Fifty-one patients were treated with clevidipine infusions, and of the 53 patients receiving standard of care, 30 received intravenous nitroglycerin infusions, and 16 were treated with nicardipine. The coprimary end point of achieving target blood pressure range occurred more often with clevidipine ($p=0.002$) and did so within a shorter median time to reach target blood pressure ($p=0.006$). When clevidipine and nicardipine were compared, the two calcium channel blockers were equally effective for blood pressure control. The secondary end point of improvement in dyspnea scores was more favorable with clevidipine at 45 minutes and up to 3 hours after initiation of therapy ($p=0.02$). There was no difference in adverse events between groups; therefore, the authors concluded that clevidipine is an effective and safe therapy for treating hypertension and improving dyspnea in ADHF. Intravenous calcium channel blockers have not been shown to improve dyspnea or hemodynamic parameters in normotensive patients presenting with volume overload. Nevertheless, the PRONTO trial introduced new data regarding the use of both clevidipine and nicardipine in patients with ADHF and concomitant hypertension (Peacock 2014).

Patient Care Scenario

G.S. is a 68-year-old man (weight 87 kg) who presents to the ED with ADHF. His vital signs include blood pressure 98/68 mm Hg and heart rate 102 beats/minute. His home drugs include bumetanide 1 mg orally twice daily, aspirin 81 mg orally daily, atorvastatin 40 mg orally daily, insulin glargine 22 units subcutaneously at bedtime, carvedilol 12.5 mg orally twice daily, and enalapril 5 mg orally twice daily.

G.S. is treated with furosemide 80 mg intravenously x 1 in the ED with only 200 mL of UOP over the next 4 hours. During this time, his blood pressure falls to 92/65 mm Hg.

ANSWER

Although his cardiac index is less than 2.2 L/minute/m², this patient has an elevated SVR, suggesting that despite the lower blood pressure, he would benefit from adding a vasodilator to optimize the cardiac index and diuretic response. Although the patient's blood pressure did decrease with the furosemide IVB dose, his current MAP is 74 mm Hg; therefore, the patient is likely to tolerate a vasodilator and experience an increase in cardiac index with a reduction in SVR. Therefore, use of an inotrope would not be necessary at this time. Adding a dopamine

The cardiology team assessing the patient decides to continue with PAC placement. The decision is made to begin a furosemide CIV at 10 mg/hour and move the patient to the cardiac ICU. G.S.'s current PAC numbers and laboratory values are as follows: PCWP 22 mm Hg, cardiac index 1.9 L/min/m², SVR 1680 dynes/s/cm⁻⁵, sodium 130 mEq/L (baseline 134 mEq/L), and SCr 1.36 mg/dL (baseline 0.98 mg/dL). The cardiology intern is concerned about G.S.'s blood pressure and cardiac index and asks you for help in initiating a vasoactive infusion to optimize the patient's cardiac index.

infusion would be inappropriate at this time, given his heart rate of 102 beats/minute and potential for worsening tachycardia with the addition of dopamine, as shown in the DAD-HF II study. According to the study evaluating the use of intravenous nitroprusside infusion in patients with a cardiac index less than 2 L/minute/m² titrating the nitroprusside to a MAP of 65–70 mm Hg, a nitroprusside infusion would be the most appropriate vasoactive medication to initiate in this patient.

1. Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol* 2008;52:200-7.
2. Triposkiadis FK, Butler J, Karayannis G, et al. Efficacy and safety of high dose furosemide versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. *Int J Cardiol* 2014;172:115-21.

INOTROPES

Despite the use of optimally dosed diuretics and add-on therapies such as intravenous vasodilators, many patients present with refractory volume overload or may have adverse effects from medication therapies. Inotrope therapies have not been prospectively studied for the treatment of volume management in ADHF, but they may be considered in patients with low systolic blood pressure, WRF, or signs of poor end-organ perfusion. Although vasodilators are preferred for adjunctive therapy for volume management in ADHF, the HFSA guidelines state that intravenous dobutamine or milrinone may be added in patients who do not respond or those who are intolerant of vasodilator therapies. In patients with invasive hemodynamic monitoring and a low CO and cardiac index despite optimization of other therapies (i.e., diuretics and vasodilators), the use of inotropes may also be considered to correct cardiac failure (Lindenfeld 2010). The management of cardiogenic shock is further discussed in the chapter on management of shock.

VASOPRESSIN RECEPTOR ANTAGONISTS

Hyponatremia (defined as serum sodium less than 135 mEqmol/L) caused by hypervolemia in patients with HFrEF is a predictor of longer hospital LOS, greater in-hospital

mortality, and greater mortality during 60- to 90-day follow-ups than in patients admitted with serum sodium greater than 135 mEq/L (Gheorghide 2007a; Klein 2005; Lee 2003). Moreover, patients with HFrEF and hyponatremia were more likely to receive inotropes, mechanical ventilation, dialysis, and mechanical ventricular support during their admission.

Established diuretic strategies, together with aggressive free water intake restriction, should be considered the mainstay of the pharmacologic management of hypervolemic hyponatremia. However, these techniques are often limited in their ability to correct hyponatremia, and the extent or rate of correction is highly variable among patients. Thus, agents targeted specifically to the correction of significant hyponatremia can be clinically useful.

Patients with ADHF have significantly elevated circulating concentrations of plasma arginine vasopressin (AVP). High AVP concentrations stimulate the vasopressin 1a (V_{1a}) and vasopressin 2 (V₂) receptors, leading to peripheral and coronary vasoconstriction (V_{1a}) and retention of water in the blood volume through effects on the renal collecting duct (V₂). Pharmacologic inhibition of the V₂ receptor leads to “aquaresis,” or the excretion of urine that is predominantly water, and a resultant increase in serum osmolality. Two agents, conivaptan and tolvaptan, exert these effects.

Table 1-6. Characteristics of Vasopressin Receptor Antagonists

Agent	Route	Dosing	Half-life	Metabolism	Cost (AWP)
Conivaptan	IV	20-mg loading dose (infused over 30 min) followed by CIV of 20–40 mg/day for 2–4 days	5–12 hr	CYP3A4	\$750/20 mg
Tolvaptan	PO	Initial: 15 mg/d, 30 mg/d (United States); 60 mg/d (Canada) Maintenance: Increase as needed after > 24 hours	4–12 hr	CYP3A4, P-glycoprotein	\$430.00–\$445.00/tablet

IV = intravenous(ly); PO = oral(ly).

Information from: Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V_{1A} and V₂ vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417-23.

Conivaptan

Conivaptan, a “nonselective” vasopressin receptor antagonist (VRA) with affinity for both the V_{1a} and the V₂ receptor, has FDA label approval for correction of hyponatremia (Table 1-6). At doses of 40–120 mg intravenously per day, conivaptan increased UOP, reduced patient weight, and increased serum sodium compared with placebo in patients with NYHA class III–IV HF (Goldsmith 2008). Despite these numeric benefits, however, these patients had no reduction in associated improvement in symptom scores at 48 hours. When studied primarily for correction of euvolemic or hypervolemic hyponatremia, conivaptan (given as 20 mg IVB, followed by 40–80 mg intravenously daily for 4 days) was significantly more effective at correcting serum sodium by 4 mEq/L at 24 hours ($p \leq 0.001$) and at producing a serum sodium greater than 135 mEq/L than was placebo ($p \leq 0.001$) while decreasing body weight and increasing net fluid loss (Zeltser 2007). In patients with a PAC, these conivaptan doses produced significant reductions in CVP and PCWP while leaving cardiac index, pulmonary artery pressure, MAP, SVR, PVR, and heart rate unchanged (Udelson 2001). This reduction in central markers of fluid status likely represents mobilization of fluid volume through a mechanism that is unique but synergistic to traditional intervention with loop and/or thiazide diuresis. Despite limited case experience of successful use of conivaptan in a patient with HF_rEF and hypervolemic hyponatremia (Pinner 2010), most clinical use of this agent tends to include correction of euvolemic hyponatremia, often because of head injury. The intravenous formulation of conivaptan is attractive for critically ill patients with strict NPO (nothing by mouth) status and/or concern for impaired gut absorption.

Tolvaptan

Tolvaptan, a selective V₂ receptor antagonist, is FDA approved for treatment of clinically significant (defined as serum sodium less than 125 mEq/L, or less than 135 mEq/L with

neurologic symptoms) hypervolemic and euvolemic hyponatremia. Tolvaptan exerts a clinical effect within 2–4 hours of administration that lasts for about 24 hours (Bhatt 2014). In several studies of patients with hyponatremia, tolvaptan improved serum sodium concentrations by about 2–4 mEq/L within 12–24 hours (Udelson 2008; Gheorghide 2007a; Schrier 2006; Gheorghide 2004) while increasing net UOP (Udelson 2008; Schrier 2006; Gheorghide 2004) and producing a net reduction in body weight of 1–2 kg (Gheorghide 2007a; Gheorghide 2004). This benefit appears to be mediated through a small but rapid reduction in CVP and PCWP, similar to that with conivaptan (Udelson 2008). Evidence of tolvaptan’s efficacy in critically ill patients requiring mechanical ventilation, having significant hypotension/hypertension, or requiring vasoactive agents such as inotropes, vasodilators, or vasopressors is limited at this time; most of these studies were conducted in less acutely ill ADHF populations. Of note, pharmacokinetic studies of crushed tolvaptan suspended in water show that absolute bioavailability may be reduced by about 25% relative to standard oral administration, with 11% of crushed medication found adhered to the nasogastric tube (McNeely 2013). Clinicians using this method of administration in critically ill patients should monitor response to dosing and consider larger doses if the expected clinical response does not occur.

Clinical Applications of VRAs

Vasopressin receptor antagonists are a potentially useful therapeutic option for patients with ADHF and concomitant hyponatremia; however, given their significant cost and limited effects on meaningful long-term ADHF outcomes, their use should be limited to very specific scenarios. Administering VRAs simply to address mild (125–134 mEq/L), asymptomatic hyponatremia cannot be recommended because most patients with HF_rEF have chronic hyponatremia with no clinical sequelae. The ACC/AHA 2013 HF guidelines recommend

VRA use only in patients with “severe” hyponatremia, volume overload, and at risk of or currently having active cognitive symptoms (Yancy 2013). The HFSA ADHF guidelines make no specific recommendation about VRA use, other than to comment that a nonselective VRA “may be reasonable” to treat hyponatremia in patients with HF and cognitive symptoms (Lindenfeld 2010). Accordingly, these agents should be viewed as no more than “add-on” to aggressive diuresis by other forms in patients with persistent and symptomatic hyponatremia, and not as initial (or even adjunctive) therapy purely for fluid removal. Many patients that present with ADHF, fluid overload, and significant hyponatremia will have some degree of correction of serum sodium with several days of aggressive loop and thiazide-mediated diuresis. It is also important to accurately determine whether a patient’s slowed mental status is the result of acutely lowered CO rather than isolated hyponatremia because patients whose CO is improved by other therapeutic modalities may have reversal of altered mental status in the absence of correction of hyponatremia. Finally, despite evidence that VRA monotherapy with tolvaptan in patients with ADHF produces UOP similar to furosemide alone (Udelson 2011), it cannot be recommended that background diuretic therapy be removed when VRAs are initiated.

Safety Issues/Use in Special Populations

Despite the potential for the clinical benefits outlined earlier, there are safety considerations with VRA use. Whether administering intravenous conivaptan or oral tolvaptan, serum sodium concentrations should be monitored several times per day to prevent sodium correction that is too rapid (defined as greater than 12 mEq/mL/day), a scenario that can lead to osmotic demyelination of nerves and worsened neurologic outcomes.

Vasopressin receptor antagonists should not be used to correct hypovolemic hyponatremia induced by traumatic blood loss or by intravascular volume depletion related to either chronic malnutrition or acute GI illness–associated nausea and/or vomiting. The patient’s volume status should be assessed, and hypovolemic hyponatremia should be corrected with an appropriate colloid or crystalloid replacement strategy.

Given that VRAs are often considered in patients who may have WRF because of renal congestion, it should be noted that conivaptan is contraindicated in patients with an eCrCl less than 30 mL/minute/1.73 m² and tolvaptan in patients with an eCrCl less than 10 mL/minute/1.73 m². Patients with HF and moderate renal dysfunction (defined as an eCrCl less than 45 mL/minute/1.73 m²) responded to tolvaptan 15-mg oral doses with UOP comparable with patients having a normal eCrCl in larger randomized trials of tolvaptan (Kida 2015). In a very small trial of patients with stage 4 or 5 chronic kidney disease (CKD), oral tolvaptan doses of 7.5–15 mg safely increased serum sodium (Otsuka 2013). In the

larger AQUAMARINE study, two days of tolvaptan 15 mg orally daily (added to loop diuretic) increased UOP by about 1500 mL without impairing renal function in patients with a baseline eCrCl of 15–60 mL/minute/1.73 m² (Matsue 2016). Doses greater than 15 mg should be used with caution in this patient population because the tolvaptan C_{max} was elevated in patients with HF compared to patients with normal renal function (Kida 2015). Although tolvaptan increased the UOP of patients receiving renal replacement therapy with peritoneal dialysis (PD), it did not meaningfully affect sodium concentrations; thus, the clinical impact of use in patients on PD seems minimal (Mori 2013). Patients with severe renal dysfunction (eCrCl less than 10 mL/minute/1.73 m²) were excluded from major clinical trials of VRAs, so use in ICU patients with severe CKD should be avoided except when benefit clearly outweighs risk and all other measures to increase serum sodium have failed.

Use of VRAs should also be limited in patients with significant hepatic dysfunction. According to the package insert, tolvaptan increases liver function tests at four times the rate of placebo in patients receiving daily doses for greater than 30 days, and cases of serious liver injury have been documented. Patients with hepatic dysfunction (other than cirrhosis) were excluded from some, but not all, major trials of tolvaptan (Gheorghiad 2007; Schrier 2006; Gheorghiad 2004), yet reported rates of new-onset liver dysfunction were rare. If VRAs are required in patients with liver dysfunction, lower doses (conivaptan 10 mg and tolvaptan 15 mg) should be considered, and doses should not be scheduled but instead limited to carefully monitored one-time administrations.

Coadministration of VRAs with potent CYP3A4 modifiers should occur with caution. Pharmacokinetic studies of patients receiving concomitant systemic ketoconazole have shown increases in tolvaptan concentrations of up to 4-fold (Bhatt 2014), and tolvaptan coadministration with the potent CYP3A4 inducer rifampicin led to tolvaptan C_{max} and AUC reduction of up to 85% (Bhatt 2014). Given these effects on the pharmacokinetics of VRAs, it is reasonable to assume that sodium correction effects are altered and that adjusted doses should be used. Moreover, despite limited pharmacokinetic data, P-glycoprotein inhibitors are likely to decrease the clearance of tolvaptan and should be used with caution, according to the package insert.

Despite the lack of data in patients with profound critical illness, it is reassuring that clinical trials of VRAs have shown no deleterious effects on blood pressure, heart rate, or organ function parameters relative to placebo, making VRAs an option in hemodynamically unstable patients. Overall, the adverse effects of VRAs do not generally differ from those of placebo, except for increased infusion-site reactions with the intravenous administration of conivaptan (Goldsmith 2008).

ULTRAFILTRATION

Background/Overview

For patients whose pharmacologic therapies fail to produce adequate volume removal, ultrafiltration (UF) is a potentially beneficial alternative. Venovenous UF allows for water extraction from blood volume as an alternative to the use of intravenous diuresis. Several prospective studies have analyzed the use of UF in patients with HFrEF and volume overload, with varying results.

Early analyses (in a very small HFrEF cohort) of short-duration UF (around 8 hours) compared with intravenous diuresis showed significant increases in net fluid removal with UF at 24 and 48 hours and trends toward greater weight loss with no appreciable adverse effects (Bart 2005). This was followed by the UNLOAD trial, a prospective, randomized trial of 200 patients with HFrEF and clear evidence of hypervolemia who received either UF or aggressive diuresis within 24 hours of admission. After 48 hours of treatment, weight loss and net fluid removal were significantly greater in the UF group, and patients receiving UF required less vasoactive support (Costanzo 2007). However, the CARRESS trial compared UF with diuresis in patients hospitalized for HFrEF with fluid overload and WRF (defined as a recent SCr increase of at least 0.3 mg/dL). This study was terminated before full patient enrollment because of significant increases in SCr and more device-related complications in the UF group with no improvements in weight loss, clinical decongestion, or patient symptoms (Bart 2012). In a subsequent, smaller trial of early UF, UF was associated with fewer subsequent HFrEF readmissions (Marenzi 2014), despite comparable body weight reduction at hospital discharge. Most recently, the largest attempted UF trial to date was terminated early because of lack of sponsor financial support, but not before showing that significantly greater fluid removal and net fluid loss in the UF group could produce a trend toward reductions in HFrEF events and/or readmission at 90 days despite an increase in device-related complications (Costanzo 2016).

Applicability of UF in HF

Despite many practical and theoretical benefits, the optimal place of UF as a tool for managing volume overload is not yet known. Ultrafiltration has the advantage of greater total sodium removal from blood, in contrast to the hypotonic urine created by diuresis, an effect that may improve the longer-term fluid balance of a patient with HFrEF. Ultrafiltration also results in less renin-angiotensin-aldosterone system up-regulation in response to fluid removal, a well-described consequence of aggressive diuresis during an ADHF admission. The greater fluid removal that commonly occurs with UF may also allow for a brief diuretic dose reduction or “holiday,” which may improve drug responsiveness when diuresis

is reinitiated. The more precise ability to titrate the rate and extent of fluid removal with UF presents an advantage over the more unpredictable response to high-intensity diuresis.

Despite these noted advantages, UF has important disadvantages. At present, data on UF show the greatest benefit from early initiation, which would require early recognition of candidates for UF in the ICU setting and programmatic commitment to consistent UF device use to achieve the best results. The cost of the devices and the personnel required to operate them present a barrier to implementation in many ICUs. The CARRESS trial shows that UF is best used before WRF occurs, although in practice, many patients are not considered for UF until 24–48 hours of aggressive diuresis has failed. Although this poor outcome may have occurred because of the “flat rate” of hourly fluid removal (200 mL/hour) and longer duration of UF (96 hours) used in this trial, it shows that the current ICU paradigm of “rescue” therapy of WRF with continuous renal replacement therapy (and fluid removal) limits the benefits of this therapy. Moreover, in several trials, patients receiving UF had significant rates of bleeding, infections, and/or vascular access issues. The requirement for systemic anticoagulation is also a potential barrier in patients with current or recent bleeding, or those deemed at high risk of bleeding because of recent surgical procedures, concomitant antiplatelet therapies, advanced age, or other factors. The location of the vascular access may also lead to increased time in bed, less willingness of staff to mobilize patients, and consequent risk of deconditioning and ICU complications.

Given the current uncertainty regarding the risk-benefit of UF in patients with ADHF, current ACC guidelines offer a class IIb, level of evidence B recommendation that UF may be considered for patients with volume overload to alleviate symptoms and lower fluid weight, primarily as salvage therapy for patients refractory to the various diuretic strategies previously described (Yancy 2013). The European Society of Cardiology guidelines make little reference to UF other than to observe that it “is usually reserved for those unresponsive or resistant to diuretics” (McMurray 2012).

CONCLUSION

Historical evidence supporting strategies for volume management in ADHF has been shown in small and heterogeneous studies. More recent randomized controlled trials have added to the literature evaluating the safety and efficacy of diuretic and add-on pharmacologic therapies. These trials have also emphasized the importance of individually tailoring medication use and weighing the risks and benefits of each therapy according to patient presentation and response. It is important that pharmacists understand the literature supporting the optimal use of both nonpharmacologic and pharmacologic strategies to guide and manage volume status in ADHF.

Practice Points

- Invasive hemodynamic monitoring should be used only when clinical assessment is insufficient to determine volume management interventions.
- Intravenous loop diuretics should be initiated in volume-overloaded patients at a dose exceeding the patient's home dose equivalent, and may be given as either intermittent boluses or continuous infusion, in order to produce an adequate response.
- When response to intravenous loop diuretics is inadequate, increasing the loop diuretic dose or adding a thiazide diuretic is reasonable.
- In patients in whom symptomatic hypotension is absent, intravenous vasodilators may be added to diuretic therapy in patients experiencing acute dyspnea.
- Parenteral inotropes may be considered patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion.
- Vasopressin receptor antagonists are a reasonable addition only in patients with significant hyponatremia and concomitant mental status changes.
- Ultrafiltration has some advantages in volume management relative to aggressive multimodal diuresis; however, conflicting clinical trial results have made the ideal scenario for its use uncertain.

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Self-Assessment Questions

1. A 66-year-old man (weight 87 kg) has a medical history of GOLD stage 3 chronic obstructive pulmonary disease, hypertension (HTN), stage 2 chronic kidney disease (CKD), heart failure with reduced ejection fraction (HFrEF) (ejection fraction [EF] 35% on echocardiography in 2014), and deep venous thrombosis (3 years ago). He presents to the ED with new-onset shortness of breath for the past 3 days. His home drugs include metoprolol succinate 25 mg orally daily, lisinopril 5 mg orally daily, tiotropium 1 inhalation daily, fluticasone and salmeterol HFA (hydrofluoroalkane) 115/21 mcg 1 puff inhaled twice daily, albuterol inhaler as needed, and furosemide 20 mg orally daily. Which one of the following tests would best discriminate the etiology of this patient's shortness of breath?
- A. Pulse oximetry monitor applied to finger
 - B. VQ (ventilation-perfusion) scan
 - C. Transthoracic echocardiogram (TTE)
 - D. N-terminal pro B-type natriuretic peptide (NT-proBNP)

Questions 2 and 3 pertain to the following case.

C.M. is a 47-year-old woman with a medical history of HTN, diabetes mellitus, and a myocardial infarction 4 years ago requiring a drug-eluting stent. She is admitted to the medical ICU with concern for sepsis. On presentation, she has blood pressure 99/64 mm Hg, heart rate 112 beats/minute, temperature 101.1°F (38.4°C), and SCr 1.4 mg/dL (baseline 1.0 mg/dL). C.M. has intermittent rigors. She is treated with early goal-directed therapy, receiving 2 L of lactated Ringer's solution, stat intravenous vancomycin and cefepime, and a norepinephrine infusion at 2 mcg/minute with improvement in her blood pressure, fever and other signs of infection. Now, 48 hours into C.M.'s admission, the organism and source have been determined, and antimicrobial therapy is tailored accordingly. She now develops mild chest pain, shortness of breath, and has heart rate of 123 beats/minute (normal sinus rhythm), and SCr of 1.7 mg/dL.

2. Which one of the following is the best first step to assess C.M.'s clinical change?
- A. Perform a coronary (left heart) catheterization.
 - B. Use TTE.
 - C. Measure a cardiac troponin.
 - D. Place a pulmonary artery catheter (PAC).
3. C.M. has acute decompensated heart failure (ADHF) with moderate left ventricular dysfunction and evidence of fluid overload. Norepinephrine is weaned to reduce systemic vascular resistance (SVR), and she is given bumetanide 1 mg intravenously twice daily for the next 48

hours. A cardiac enzyme panel (creatinine kinase, creatine kinase-MB fraction, and troponin) is negative. During this time, her heart rate has fallen to 105 beats/minute, fluid balance is 4 L net negative, and SCr is 1.3 mg/dL. Which one of the following would be best to assess C.M.'s treatment response?

- A. Use cardiac catheterization.
 - B. Insert a PiCCO catheter.
 - C. Place a pulmonary artery catheter (PAC).
 - D. No invasive monitoring is required.
4. A 47-year-old man presents to the cardiac ICU with worsening dyspnea, fatigue, and altered mental status over the past 7 days. His medical history includes HFrEF with an EF of 10%–15% (last checked 6 months ago), stage 3 CKD, hyperlipidemia, hypothyroidism, and atrial fibrillation. On admission he has blood pressure of 88/60 mm Hg, heart rate 112 beats/minute, serum Na 126 mEq/L, BUN 55 mg/dL, SCr 1.9 mg/dL, Hgb 9.6 g/dL and Hct 28.0%. The patient has 1+ lower extremity edema, but chest radiography does not reveal significant bilateral opacities. The decision is made to place a PAC to determine cardiac output (CO), intravascular volume status, and need for inotropic therapy. The PAC produces the following values: CO 3.4 L/minute, cardiac index 1.7 L/minute/m², CVP 9 mm Hg, pulmonary artery systolic pressure/pulmonary artery diastolic pressure 56/32 mm Hg, pulmonary capillary wedge pressure (PCWP) 17 mm Hg, and SVR 1287 dynes/second/cm⁻⁵. Which one of the following is best to recommend first for this patient?
- A. Furosemide infusion at 10 mg/hour, goal net fluid status: negative 3 L/day
 - B. Dobutamine 2.5 mcg/kg/minute, goal cardiac index: 2.0–2.2 L/minute/m²
 - C. Nitroglycerin infusion 30 mcg/minute, goal SVR 800–1200 dynes/second/cm⁻⁵
 - D. Nitroprusside infusion 1 mcg/kg/minute, goal SVR 800–1200 dynes/second/cm⁻⁵

Questions 5–7 pertain to the following case.

H.H. is a 46-year-old man with non-ischemic cardiomyopathy, atrial fibrillation, and hypothyroidism. He presents to the heart failure (HF) clinic for a routine follow-up. H.H. has been sleeping with two pillows at night and has been unable to climb the stairs from first to second floor for the past 10 days because of fatigue and shortness of breath. On physical examination, H.H. has 3+ pitting edema with rales heard on auscultation. His home drugs include lisinopril 5 mg orally daily, metoprolol succinate 75 mg orally daily, bumetanide 1 mg orally twice

daily, levothyroxine 50 mcg orally daily, and warfarin dosed by clinic (goal INR 2–3). His blood pressure is 105/72 mm Hg and heart rate is 78 beats/minute and all labs findings are within normal limits including a SCr 1.1 mg/dL. The clinic physician decides to admit H.H. for ADHF treatment.

5. Which one of the following is best to recommend as the initial diuretic dose for H.H.?
 - A. Furosemide 40 mg intravenously daily
 - B. Bumetanide 1 mg intravenously twice daily
 - C. Furosemide 100 mg intravenously twice daily
 - D. Furosemide continuous infusion at 20 mg/hour
6. At 48 hours into admission, H.H. is net negative 500 mL daily. His daily loop diuretic dose is increased by 50%, and his net urinary output (UOP) increases to 750 mL net negative daily. He has 2+ pitting edema with rales on examination. You point out to the multidisciplinary team that H.H. is 7 kg above his dry weight. Current vital signs are blood pressure 108/76 mm Hg and heart rate 86 beats/minute. Which one of the following would best promote further diuresis in H.H.?
 - A. Change intravenous furosemide to equivalent doses of intravenous bumetanide
 - B. Add dopamine infusion at 2 mcg/kg/minute
 - C. Obtain a pulmonary artery catheter (PAC) to guide therapy
 - D. Add oral metolazone 2.5 mg
7. Over the next 48 hours, H.H. is net negative 2.2 L and has lost 1.7 kg in body weight. His blood pressure is now 113/81 mm Hg, heart rate 82 beats/minute, SCr 1.2 mg/dL, and Na 128 mEq/L (increased from 125mEq/L the day prior). H.H. is starting to feel better and would like to be discharged to get back to work. The ICU fellow would like to prescribe conivaptan 20 mg intravenous bolus (IVB) and 40 mg/day intravenous infusion to enhance diuresis and increase H.H.'s sodium closer to his baseline. Which one of the following is best alternative to recommend for H.H.?
 - A. Give tolvaptan 15 mg orally once today, then daily for 7 days after discharge.
 - B. Give 24 hours of ultrafiltration (UF).
 - C. Give metolazone 5 mg orally once.
 - D. Add spironolactone 25 mg orally daily.

Questions 8–10 pertain to the following case.

M.B. is a 62-year-old woman with a history of ischemic cardiomyopathy, HTN, diabetes, and hypothyroidism. She is admitted through the ED after 3 days of worsening shortness of breath and dyspnea on exertion. Her weight is up 8 kg from her last clinic visit. Her home drugs include carvedilol 12.5 mg orally twice daily, aspirin 81 mg orally daily, atorvastatin

40 mg orally daily, glipizide 5 mg orally twice daily, enalapril 5 mg orally twice daily, furosemide 100 mg orally twice daily, and levothyroxine 125 mcg orally daily. Current laboratory test results are Na 129 mEq/L, K 3.8 mEq/L, Cr 1.62 mg/dL, and albumin 2.9 g/dL. M.B.'s vital signs on admission are blood pressure 101/68 mm Hg and heart rate 102 beats/minute.

8. The admitting service would like to initiate M.B. on intravenous diuretics. They ask you about using a continuous infusion of furosemide. Which one of the following is best to recommend for M.B.?
 - A. Initiate furosemide 5 mg/hour with nesiritide 0.001 mcg/kg/minute
 - B. Initiate a furosemide infusion at 20 mg/hour
 - C. Initiate IVB furosemide 80 mg intravenously twice daily
 - D. Initiate furosemide 5 mg/hour with dopamine 5 mcg/kg/minute
9. The cardiologist wishes to add nesiritide to M.B.'s ADHF therapies because she still has dyspnea. Which one of the following is best to recommend regarding the use of nesiritide for M.B.?
 - A. According to the ASCEND trial, nesiritide increases the risk of hypotension without affecting the rates of dyspnea or hospitalizations for HF.
 - B. According to the ASCEND trial, use of nesiritide 0.005 mcg/kg/minute is safe and effective for ADHF management.
 - C. According to the ROSE-HF trial, dopamine 2 mcg/kg/minute should be initiated instead of nesiritide because it better manages volume overload.
 - D. According to the ROSE-HF trial, nesiritide 0.005 mcg/kg/minute has better hemodynamic effects in ADHF than nesiritide 0.01 mcg/kg/minute.
10. At 72 hours into the admission, M.B.'s UOP has produced only a net negative 500-mL balance. Current vital signs are blood pressure 115/72 mm Hg, heart rate 98 beats/minute and respiratory rate 22 respirations/minute with poor oxygenation despite 4 L of oxygen by nasal cannula. The patient continues to experience progressive shortness of breath. The team wants to initiate therapy to relieve M.B.'s acute dyspnea. Which one of the following is best to recommend adding to M.B.'s regimen?
 - A. Dopamine 2 mcg/kg/minute
 - B. Dopamine 5 mcg/kg/minute
 - C. Nitroglycerin 20 mcg/minute infusion
 - D. Dobutamine 5 mcg/kg/minute
11. You are working with a team of HF physicians and nurse practitioners to develop a guideline for the diuretic

management of patients with ADHF. The team has asked you to address the use of thiazide and thiazide-like diuretics for add-on therapy. Which one of the following statements would be best to add to the guideline?

- A. Intravenous chlorothiazide is superior to oral thiazide diuretics and is preferred despite higher cost.
 - B. Adding a thiazide diuretic is more effective for increasing UOP than increasing loop diuretic doses.
 - C. Oral thiazide and thiazide-like diuretics are associated with a lower risk of hypokalemia compared to intravenous chlorothiazide.
 - D. Oral thiazide and thiazide-like diuretics have similar effects on diuresis compared to intravenous chlorothiazide.
12. A 72-year-old woman is admitted for ADHF. She is initiated on a furosemide infusion at 10 mg/hour. At 48 hours, her net UOP is negative 1250 mL/day, and the team adds hydrochlorothiazide 25 mg oral daily. After 24 hours, the patient is net negative 2250 mL, with blood pressure 116/75 mm Hg, heart rate 80 beats per minute, and respiratory rate 18 respirations per minute with optimal oxygenation on room air. Based upon physical exam findings, the team suspects the patient has an additional 3-4 kg of fluid overload and asks if you recommend any changes to the current regimen. Which one of the following is best to recommend for this patient?
- A. Discontinue hydrochlorothiazide 25 mg/day and add intravenous chlorothiazide 500 mg daily
 - B. Add nitroglycerin 40 mcg/minute
 - C. Continue present treatment
 - D. Add nesiritide 0.01 mcg/kg/minute
13. A 50-year-old man is admitted to the ICU for ADHF. The patient was initiated on furosemide continuous infusion at 15 mg/hour. Due to minimal UOP, he received chlorothiazide 500 mg intravenously x 1 overnight. On rounds the next day, you note that the patient has only made 1 L of urine since admission. His blood pressure is 95/65 mm Hg and heart rate is 115 beats/minute. Current laboratory test results are Na 133 mEq/L, K 3.3 mEq/L, and SCr 1.66 mg/dL. The decision is made to insert a PAC to further guide management. The PAC reveals CO 3.5 L/minute, cardiac index 1.7 L/minute/m², PCWP 28 mm Hg, SVR 1800 dynes/second/cm⁻⁵, and CVP 13 mm Hg. Which one of the following is best to recommend for this patient?
- A. Add nitroprusside infusion with target mean arterial pressure (MAP) 65–70 mm Hg.
 - B. Add dopamine 5 mcg/kg/minute.
 - C. Repeat chlorothiazide 500 mg intravenously x 1.
 - D. Increase furosemide infusion to 20 mg/hour.

14. A 60-year-old woman was admitted 48 hours ago for ADHF. In the first 24 hours, she was net negative 1.5 L with intravenous loop diuretics alone. However, over the past 24 hours she is net negative 0.5 L with furosemide 120 mg intravenously every 8 hours and metolazone 2.5 mg orally x 1 dose. Current laboratory test results include Na 131 mEq/L, K 3.7 mEq/L, and SCr 1.8 mg/dL. Her vital signs are blood pressure 91/63 mm Hg and heart rate 82 beats/minute. Which one of the following is best to recommend for this patient?
- A. Give metolazone 10 mg orally x 1 dose
 - B. Change to furosemide continuous infusion 7.5 mg/hour
 - C. Give tolvaptan 15 mg orally daily
 - D. Give nesiritide 0.005 mcg/kg/minute

Questions 15–17 pertain to the following case.

P.T. is a 45-year-old man admitted to the ED with progressive shortness of breath and fatigue. He is symptomatic at rest, and although he has been feeling poorly for the past 2 weeks, he admits having missed his home medications for the past 48 hours. His medical history is significant for HTN, nonischemic cardiomyopathy, and diabetes. His home medications include lisinopril 20 mg orally daily, carvedilol 25 mg orally twice daily, spironolactone 25 mg orally daily, bumetanide 3 mg orally twice daily, metolazone 2.5 mg orally weekly, and insulin glargine 30 units subcutaneously at bedtime. P.T. is admitted to the cardiac ICU and initiated on a furosemide continuous intravenous infusion at 10 mg/hour. His vital signs on admission are blood pressure 126/87 mm Hg and heart rate 76 beats/minute. P.T.'s pertinent laboratory test results are SCr 1.2 mg/dL and Na 128 mEq/L.

15. At 24 hours into admission, P.T.'s fluid balance is net negative 750 mL with a furosemide 10 mg/hr continuous infusion. The team has decided to increase the dose of furosemide to 20 mg/hr. If his target UOP is not met with this therapy, which one of the following would be best to add next for P.T.?
- A. Dobutamine 2.5 mcg/kg/min
 - B. Chlorothiazide 500 mg intravenously x 1
 - C. Milrinone 0.2 mcg/kg/minute
 - D. Dopamine 5 mcg/kg/minute
16. P.T. is net negative 1.5 L over the next 48 hours. His current blood pressure is 116/80 mm Hg, heart rate is 72 beats/minute, BUN is 27 mg/dL, and SCr is 1.5 mg/dL. His serum sodium has fallen from 128 mEq/L to 121 mEq/L, and his nurse reports that he is less responsive than when she last took care of him 3 days ago. When the multidisciplinary team visits during rounds, P.T. calls his brother by the wrong name and indicates that he is at his

local grocery store. Which one of the following is best to recommend for P.T.?

- A. Add dopamine 5 mcg/kg/minute.
 - B. Add tolvaptan 15 mg orally.
 - C. Initiate UF with fluid removal goal of 2 L per day x 48 hours.
 - D. Add metolazone 2.5 mg orally daily.
17. After 48 hours, P.T. is an additional 2 L net negative, his blood pressure is 120/83 mm Hg, heart rate is 80 beats/minute, BUN is 23 mg/dL, SCr is 1.3 mg/dL, and Na is 127 mEq/L. The multidisciplinary team is ready to transition P.T. to an oral diuretic regimen and a lower level of care. Which one of the following is best to recommend for P.T. as he leaves your care?
- A. Bumetanide 4 mg orally twice daily with metolazone 2.5 mg as needed up to 3 days a week
 - B. Bumetanide 2 mg orally twice daily with tolvaptan 30 mg orally daily
 - C. Bumetanide 2 mg orally twice daily
 - D. Tolvaptan 30 mg orally daily
18. Your hospital is considering resource allocation to allow for routine use of UF in patients who present to critical care areas with ADHF. You are asked to help develop an algorithm that would identify the best use of this modality. Which one of the following is best to include in your edits to the draft of the algorithm?
- A. UF should be initiated in all patients with ADHF who have received a minimum dose of intravenous loop diuretic of 480 mg of furosemide equivalents and are not achieving fluid output goals.
 - B. UF should be used for a maximum of 8 hours in any single patient per admission.
 - C. Patients with current or recent bloodstream infections and/or bleeding events should not be initiated on UF.
 - D. UF should be used for a minimum of 96 hours in any single patient per admission.
19. A 76-year-old woman is admitted with shortness of breath, dyspnea on exertion, and significant pulmonary edema. Her current weight is 56 kg, increased from her stated dry weight of 50 kg. Her BUN is 34 mg/dL, SCr is 1.3 mg/dL, and Na is 126 mEq/L (baseline 129 mEq/L). Her home medications include furosemide 40 mg orally twice daily, losartan 25 mg orally daily, and spironolactone 25 mg orally daily. After 24 hours of furosemide 80 mg intravenously twice daily, the patient is 300 mL

net positive and her SCr has increased from 1.3 mg/dL to 1.5 mg/dL. She does not note any symptomatic improvement. Which one of the following is best to recommend for this patient?

- A. Initiate UF at 200 mL/hr.
 - B. Initiate dobutamine at 5 mcg/kg/minute.
 - C. Change to furosemide 20 mg/hour infusion.
 - D. Give tolvaptan 15 mg orally once.
20. A 78-year-old woman (weight 70 kg) presents to the trauma ICU with several fractures and significant blood loss incurred during a motor vehicle crash. Her medical history includes HF_{rEF}, HTN, osteoporosis, seizure disorder, and stage 5 CKD (baseline SCr 3.7 mg/dL). Her home medications include metoprolol succinate 50 mg orally daily, hydralazine 25 mg orally three times daily, vitamin D 50,000 units orally weekly, phenytoin 200 mg orally daily, and calcium acetate 667 mg orally three times daily with meals. After aggressive fluid resuscitation with blood transfusions and crystalloid totaling 5 L during the first 24 hours of admission, the patient's serum Na has fallen to 123 mEq/L (132 mEq/L on admission). Her blood pressure is 91/63 mm Hg and heart rate is 66 beats/minute. The team wants to correct her sodium concentration with conivaptan 20 mg intravenously once, followed by 40 mg intravenously daily for 4 more days. Which one of the following is best to recommend regarding the use of conivaptan in this patient?
- A. The dose should be decreased to 10 mg intravenously once, followed by 20 mg intravenously daily.
 - B. It is unclear that conivaptan will be effective in correcting the patient's serum sodium.
 - C. Conivaptan may worsen the patient's existing hypotension.
 - D. Conivaptan has a greater rate of adverse effects such as hepatic dysfunction in patients her age.

Learner Chapter Evaluation: Volume Management in Acute Decompensated Heart Failure.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish between hypervolemia, hypovolemia, and euvolemia in acute decompensated heart failure (ADHF) on the basis of hemodynamic parameters.
13. Interpret the results of invasive monitoring to create a pharmacologic treatment plan to improve the hemodynamic status of a patient with ADHF.
14. Evaluate the role of intravenous vasodilators as add-on therapy for the management of hypervolemia in ADHF.
15. Evaluate the usefulness of vasopressin receptor antagonists in hypervolemic hyponatremia.
16. Devise a volume management strategy using ultrafiltration in ADHF.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:



Advanced Heart Failure

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LEARNING OBJECTIVES

1. Design optimal pharmacotherapy for patients awaiting left ventricular assist device (LVAD) or implantation or orthotopic heart transplantation (OHT).
2. Construct safe and effective drug therapy regimens for patients receiving extracorporeal membrane oxygenation support.
3. Devise effective thromboprophylactic strategies for patients receiving percutaneous LVAD support.
4. Design effective treatment plans for patients with complications of durable LVAD therapy.
5. Devise safe and effective pharmacotherapy regimens in patients recovering from OHT.

ABBREVIATIONS IN THIS CHAPTER

ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
CF-LVAD	Continuous-flow left ventricular assist device
CMV	Cytomegalovirus
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
HF	Heart failure
IABP	Intra-aortic balloon pump
LV	Left ventricle
LVAD	Left ventricular assist device
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
OHT	Orthotopic heart transplantation
PCWP	Pulmonary capillary wedge pressure
pVAD	Percutaneous left ventricular assist device
PVR	Pulmonary vascular resistance
RV	Right ventricular
Svo ₂	Mixed venous oxygen saturation
TEG	Thromboelastography
UFH	Unfractionated heparin
VA	Venoarterial

Table of other common abbreviations.

INTRODUCTION

Despite advances in pharmacotherapy and device technology (e.g., implantable cardioverter-defibrillator and cardiac resynchronization therapy), heart failure (HF) remains a leading cause of morbidity and mortality in both the United States and around the world. This is particularly prominent with advanced HF (i.e., stage D), which carries about a 90% 1-year mortality rate without heart transplantation or left ventricular assist device (LVAD) implantation (Mehra 2012). This subset of patients with advanced disease often continues to progress and develop persistently severe symptoms at rest or with minimal activity, despite conventional HF drug therapy regimens. Such advanced disease may eventually require admission to the ICU for aggressive stabilizing measures such as mechanical ventilation, fluid removal (including ultrafiltration), and intravenous inotrope therapy.

Criteria for Advanced HF

Although various criteria have been proposed to characterize advanced HF, no one diagnostic test can identify these patients. Rather, a combination of biomarkers, physical examination findings, laboratory data, and functional capacity allow for an assessment of disease severity. The American College of Cardiology/American Heart Association has defined these patients as those “with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support (MCS), procedures to facilitate fluid removal, continuous positive inotropic infusions, or cardiac

transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice” (Yancy 2013). The European Society of Cardiology has created a list of objective criteria that can be useful in recognizing patients with advanced HF (Box 2-1). The clinical pharmacist should be familiar with these criteria to anticipate and recommend medication-based therapies to improve symptoms and/or hemodynamics. The presence of advanced disease influences the overall goals of care and treatment approach for patients with HF in the ICU. For instance, a patient with stage C disease who is admitted to the ICU with acute HF and renal injury may require a short-term course of inotrope- or vasodilator-assisted diuresis, whereas a patient with stage D disease might require long-term vasoactive therapy as a bridge to either a durable LVAD or an orthotopic heart transplant (OHT).

Candidacy for LVAD and OHT

The evaluation process for advanced HF treatment modalities is complex and beyond the scope of this chapter. Although international guidelines have proposed suggestions for which patients should be considered for these therapies,

Box 2-1. European Society of Cardiology Definition of Advanced HF

1. Severe symptoms of HF at rest (NYHA class 4)
2. Episodes of pulmonary or systemic congestion and/or reduced cardiac output at rest
3. Objective evidence of severe cardiac dysfunction as shown by at least one of the following: LVEF < 35%; pseudo-normal or restrictive mitral inflow pattern; mean PCWP > 16 mm Hg and/or RAPs > 12 mm Hg; or high BNP or NT-proBNP plasma concentrations
4. Severe impairment of functional capacity as shown by one of the following: inability to exercise; 6-min walk distance \leq 300 m; peak Vo_2 < 12–14 mL/kg/min
5. History of > 1 hospitalization in past 6 mo
6. Presence of all the previous features despite “attempts to optimize” therapy, including diuretics and guideline-directed medical therapy, unless poorly tolerated or contraindicated

BNP = B-type natriuretic peptide; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

Information from: Metra M, Ponikowski P, Dickstein K, et al. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2007;9:684-94.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of acute decompensated heart failure
- Hemodynamic profile of cardiogenic shock
- Stages and classification of heart failure with a reduced ejection fraction
- Pharmacology of agents commonly used to treat patients with heart failure, including diuretics, vasodilators, and positive inotropic agents
- Basic pharmacology of drug therapy agents specific to LVAD and OHT patients (e.g., anticoagulants and immunosuppressive agents)

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- [2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines](#). *Circulation* 2013;128:e240-e319.
- European Society of Cardiology. [ESC Clinical Practice Guidelines: Acute and Chronic Heart Failure](#). 2016 [homepage on the Internet].

each institution ultimately develops its own listing criteria according to the center’s volume and tolerance for treating complex patients. Table 2-1 contains examples of common inclusion and exclusion criteria for both OHT and durable LVAD. Although some prohibiting conditions are common to both options (e.g., limited life expectancy or severe pulmonary disease), others are uniquely exclusive (e.g., severe right ventricular [RV] failure would preclude a durable LVAD, but not OHT). In addition, some OHT contraindications may improve or resolve during LVAD support (e.g., pulmonary hypertension or obesity). Patients may initially receive an LVAD as destination therapy with the eventual plan of reevaluating their transplant candidacy later. Finally, the critical care practitioner must remember the grim prognosis for patients with advanced HF who are not candidates for either OHT or durable LVAD therapy and guide the overall drug therapy strategy toward palliative care, should the ICU patient be deemed ineligible for both.

MEDICAL MANAGEMENT OF END-STAGE HF

Hemodynamic Optimization of the Pre-LVAD or Pre-OHT Patient

Most patients with stage D HF are refractory to guideline-directed medical therapy (e.g., β -blockers), and medicinal options are generally limited. For ambulatory patients awaiting OHT or durable LVAD, the American College of Cardiology/American Heart Association guidelines suggest that

Table 2-1. Indications and Contraindications for Heart Transplant and Durable LVAD Therapy

	Heart Transplant	Durable LVAD
Indications	<ul style="list-style-type: none"> • Cardiogenic shock requiring continuous inotropic support or temporary MCS • Persistent NYHA class IV HF symptoms refractory to maximal medical therapy (LVEF < 20%; peak oxygen consumption < 12 mL/kg/min) • Intractable angina not amenable to revascularization • Intractable arrhythmias 	<ul style="list-style-type: none"> • NYHA class IV HF symptoms • LVEF < 25% • Failure to respond to optimal medical management for at least 45 of the past 60 days • IABP-dependent for 7 days • Intravenous inotrope dependence for 14 days • Functional limitation with peak oxygen consumption < 14 mL/kg/min
Contraindications	<ul style="list-style-type: none"> • Systemic illness with life expectancy < 2 yr (malignancy, AIDS, lupus) • COPD with FEV₁ < 1 L/min • Clinically severe cerebrovascular disease • Fixed pulmonary arterial hypertension (e.g., PVR > 3 Wood units) • Renal dysfunction with eGFR < 30 mL/min/1.73 m^{2a} • Age > 70^a • Active infection (not LVAD related) • Peptic ulcer disease^a • Diabetes with end-organ damage (e.g., neuropathy) or poor glycemic control (A1C > 7.5%)^a • Peripheral vascular disease^a • Morbid obesity (BMI > 35 kg/m²)^a • Active mental illness or dementia^a • Inadequate social support^a • Drug or tobacco use within 6 mo • HIT within 100 days^a 	<ul style="list-style-type: none"> • Morbid obesity^a • Small body (BSA < 1.5 m²)^a • CKD^a • Mild-moderate hepatic dysfunction^a • Malnutrition^a • Sepsis or active infection • Severe right HF • Severe carotid artery disease • Severe COPD • Severe CVA with deficit • Hemodialysis • Persistent coagulopathy • Noncardiac illness with limited life expectancy • HF expected to recover without durable LVAD

^aDenotes a more relative contraindication.

BSA = body surface area; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; FEV₁ = forced expiratory volume in 1 second; eGFR = estimated glomerular filtration rate; HF = heart failure; HIT = heparin-induced thrombocytopenia; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; MCS = mechanical circulatory support; NYHA = New York Heart Association; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance. Information from: Owens AT, Jessup M. Should left ventricular assist device be standard of care for patients with refractory heart failure who are not transplantation candidates?: left ventricular assist devices should not be standard of care for transplantation-ineligible patients. *Circulation* 2012;126:3088-94.

continuous intravenous positive inotrope therapy is reasonable as a “bridge therapy” (class IIa, level of evidence B). Once patients enter the hospital, the goals of therapy shift toward hemodynamic optimization and preservation of other end-organ function in preparation for OHT or LVAD surgery. Patients who are volume overloaded should be decongested aggressively with intravenous loop diuretics, with a goal of normalizing both right- and left-sided filling pressures. Those who require ICU admission may also require a pulmonary artery catheter to more carefully guide treatment and achieve hemodynamic goals.

Patients with low cardiac output or overt cardiogenic shock should receive inotropic therapy with either milrinone or dobutamine. Restoration of organ perfusion and reversal of shock before surgery are paramount, particularly for patients

with LVAD, who have a 30%–50% higher mortality rate when hemodynamically unstable at the time of device implantation (Kirklin 2015). There is no evidence to suggest that one inotropic agent is preferred to another as a bridge to OHT or durable LVAD; hence, this choice should be guided according to the patient’s response and potential for toxicity (e.g., tachycardia or tachyphylaxis with dobutamine) or according to pharmacokinetic considerations (e.g., renal failure with milrinone). Combination inotropic support with a β -receptor agonist and a phosphodiesterase inhibitor may offer additive efficacy and facilitate lower doses of each agent, which may minimize drug toxicity (Meissner 1992). Dopamine should generally be avoided in these patients because of its extremely unpredictable pharmacokinetic profile (MacGregor 2000), together with its potentially higher mortality rate

compared with norepinephrine in patients with cardiogenic shock (De Backer 2010). When faced with concomitant hypotension (mean arterial pressure [MAP] less than 65 mm Hg), clinicians can consider monotherapy with epinephrine, which has inotropic and vasoconstricting properties. Alternatively, limited evidence suggests that the combination of a vasopressor agent (e.g., norepinephrine) and an inotrope (e.g., dobutamine) is safer and more effective than epinephrine monotherapy in patients with hypotension and cardiogenic shock (Levy 2011).

In preparing patients with advanced HF in the ICU for either OHT or durable LVAD surgery, the critical care pharmacotherapist should consider de-escalating traditional HF medications. This is particularly true for angiotensin-converting enzyme (ACE) inhibitors, which may be harmful in patients undergoing cardiac surgery. In a recent propensity-score matched cohort of over 7000 patients undergoing coronary artery bypass grafting surgery, preoperative ACE inhibitor exposure was associated with a higher risk of death and postoperative renal dysfunction (Miceli 2009). Although the precise mechanism for these deleterious effects is unclear, it is postulated that preoperative ACE inhibitor exposure contributes to vasoplegia, hypotension, and an increase in vasopressor requirements postoperatively. Given these findings, ICU clinicians should consider discontinuing ACE inhibitor therapy in patients who are listed for OHT or in those who are scheduled for durable LVAD implantation. Clinicians should remember that the goals of care in this situation are hemodynamic optimization, preservation of end-organ function, and minimization of operative risk. In addition, ACE inhibitor therapy provides a long-term mortality benefit, which is not as relevant in this scenario.

Management of Anticoagulation and Antiplatelet Therapy

In preparing ICU patients for either OHT or durable LVAD implantation, the clinical pharmacist should focus on discontinuing long-acting anticoagulants and transitioning to intravenous unfractionated heparin (UFH). This is especially true in patients listed for OHT because donor offers can come at any time, and there are usually only a few hours to prepare the patient for surgery. When treating a patient with therapeutic anticoagulation who requires urgent reversal for OHT, current guidelines advocate the use of intravenous vitamin K in conjunction with fresh frozen plasma, prothrombin complex concentrates (PCCs), or recombinant factor VII (Costanzo 2010).

Cessation of antiplatelet therapy is a more difficult scenario, specifically in those with recent coronary artery stenting who require dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor antagonist. Preoperative clopidogrel exposure has consistently been shown to increase the risk of postoperative bleeding in cardiac surgery patients. The risk of pericardial tamponade or reoperation for bleeding

is increased when surgery is performed less than 24 hours after clopidogrel discontinuation (Hermann 2010). Between 1 and 4 days, clopidogrel preexposure increases the need for transfusion, with the risk diminishing after each additional day. Although ticagrelor's surgical bleeding profile is similar to that of clopidogrel, prasugrel carries a substantially higher risk and thus should not be used in patients listed for OHT or those slated for a durable LVAD implant (Wiviott 2007). Cangrelor, a non-thienopyridine intravenous antagonist of the P2Y₁₂ receptor, was effective in the BRIDGE trial at maintaining platelet inhibition in the perioperative setting for patients undergoing coronary artery bypass grafting surgery (Angiolillo 2012). However, this trial was underpowered to evaluate clinical end points; therefore, the usefulness of this agent as a "bridge" therapy in patients awaiting an OHT or an LVAD implant remains unknown. Preoperative bridging with a glycoprotein IIb/IIIa inhibitor has been described in several case reports and case series and suggest a high residual risk of stent thrombosis and a high rate of bleeding (Warshauer 2015). Thus, these medications should not be considered for use in perioperative bridging.

In sum, when treating a patient with pre-OHT or pre-LVAD having an indication for a P2Y₁₂ receptor antagonist, the ICU pharmacotherapist and multidisciplinary team must evaluate the overall risk of stent thrombosis and surgical bleeding and make decisions regarding continuation of antiplatelet therapy on a case-by-case basis. In addition to clinical factors, the anticipated bridging time must be considered because of the high cost of cangrelor. When the time to surgery may be prolonged (e.g., common blood type), use of cangrelor may be cost-prohibitive.

EXTRACORPOREAL MEMBRANE OXYGENATION

Indications for and Types of ECMO

Extracorporeal membrane oxygenation (ECMO) is a form of acute temporary MCS capable of fully replacing cardiopulmonary circulation in patients with severe cardiac and/or pulmonary dysfunction. A typical ECMO circuit is composed of a pump, semipermeable membrane oxygenator, and heat exchanger. The system can provide full circulatory support, augment or enhance gas exchange, and control body temperature to facilitate therapeutic hypothermia. Because ECMO has several potential indications, the configurations of cannulation can vary to best serve a patient's specific needs. Patients with cardiac arrest or refractory cardiogenic shock are candidates for full circulatory support with venoarterial (VA) ECMO (Figure 2-1). Cannulation strategies may be confined to peripheral vessels (peripheral ECMO), or they may be cannulated centrally (directly to vena cava and/or the aorta) when the patient cannot wean from the cardiopulmonary bypass circuit after surgery. In centrally cannulated ECMO, patients are usually left with an open

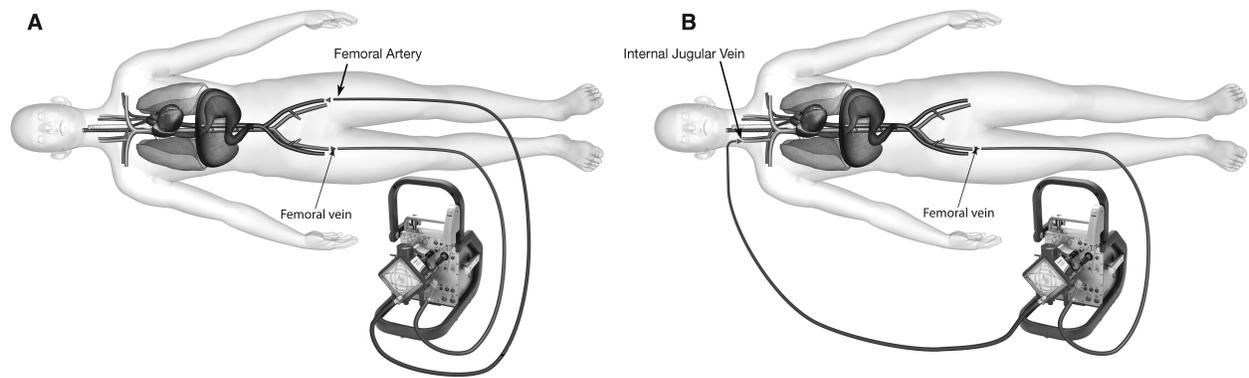


Figure 2-1. A. Peripheral venoarterial extracorporeal membrane oxygenation (ECMO) configuration indicated in refractory cardiogenic shock or cardiopulmonary arrest. B. Peripheral venovenous ECMO configuration indicated in refractory respiratory failure without circulatory compromise.

Reprinted with permission from Maquet GmbH & Co., KG (Rastatt, Germany).

chest, making this strategy less appropriate for extended duration of support.

In the population with advanced HF, ECMO is generally considered a form of MCS that is initiated when the patient's circulatory status is either not improving or potentially declining despite the use of vasoactive medications with or without intra-aortic balloon pump (IABP) therapy. Extracorporeal Life Support Organization (ELSO) registry data reported in July 2016 show current survival to discharge of adult patients with cardiac dysfunction who undergo extracorporeal life support to be 41% (ELSO Registry). Depending on the institution's capabilities, ECMO may be the only available temporary MCS.

In patients with cardiogenic shock unresponsive to medical therapy, VA ECMO is intended to serve as a bridge to recovery of native cardiac function, a more durable form of MCS, or, in some cases, a bridge to OHT. Because of the underlying critical nature of patients requiring VA ECMO, bridge to durable MCS is generally preferred – if the patient is deemed eligible during ECMO weaning – to bridge to transplant because of the risk of poor OHT outcomes in such critically ill patients.

Hemodynamic Consequences of ECMO

Using VA ECMO can dramatically augment the oxygenation and circulation of blood in a patient with cardiogenic shock. Because the pumps used in most modern ECMO circuits are centrifugal continuous flow, diminished (or loss of) pulsatility can be expected. Because the ECMO will account for a significant portion of total cardiac output, native cardiac output may be diminished to the point that the aortic valve no longer opens. As flow from the ECMO continues throughout each cardiac cycle, diastolic pressure is expected to be higher than

thought in a patient with the same underlying physiology not receiving ECMO support.

Typically, many positive inotropic and vasopressor medications are actively being administered when initiating VA ECMO, but on initiation, the clinical pharmacist should actively monitor and potentially taper vasopressor agents, targeting a minimum MAP to adequately perfuse vital organs (typically 60–65 mm Hg). Positive inotropic therapy may at times be continued during ECMO support to sustain aortic valve opening and ejection of blood from the left ventricle (LV) in order to minimize the risk of intracardiac and aortic root thrombus formation. Positive inotropic agents may also facilitate weaning of ECMO support if initiated amid cardiac arrest in a patient with severely impaired contractility (ELSO 2013). The clinical pharmacist should monitor for malignant arrhythmias and consider discontinuing β -adrenergic agonists if electrical instability precludes weaning ECMO support. In some cases, patients may be hypertensive after ECMO support is initiated because of elevated systemic vascular resistance. Episodes of hypertension should warrant investigation of appropriate sedation and analgesia to ensure that neither pain nor agitation is driving a hyperadrenergic blood pressure response. If these alternative causes of systemic hypertension have been addressed, afterload reduction should be considered with continuous infusion vasodilating agents (nicardipine, nitroglycerin, nitroprusside) to target a MAP of less than 90 mm Hg, which will improve the flow offered by the ECMO circuit. Negative inotropic antihypertensive agents (diltiazem, esmolol, labetalol) should be avoided, if possible, in patients receiving ECMO as the result of cardiogenic shock because these may negatively affect the patient's ability to be weaned from temporary support.

Complications of ECMO Therapy

The primary complications encountered during ECMO support depend largely on the configuration of ECMO; however, there are some common complications irrespective of cannula placement. One of the most worrisome risks of all forms of MCS is thromboembolic events. A clot within the VA ECMO circuit could potentially lead to thrombi embolizing to the cerebral and systemic circulation, causing ischemic stroke limbs, or internal organs. These risks are ever-present, even with the most meticulous anticoagulation, which should prompt timely weaning of ECMO once the patient has recovered or is transitioning to a more durable form of MCS. Local thrombotic complications within the ECMO circuit may also contribute to the mechanical failure of the device. Detection of thrombosis within the circuit may necessitate exchanging the circuit to avert more catastrophic events and avoid unnecessary transfusion of platelets and other blood products, which may be consumed within a thrombosing ECMO circuit and oxygenator.

Because of the large size of the inflow and outflow intravascular cannulas inserted into major blood vessels together with any effects of the machine on blood components, bleeding is another potentially devastating complication of ECMO therapy. The risk of hemorrhage can be compounded by any existing coagulopathy, which is common in patients with cardiogenic shock, and further exacerbated by the use of parenteral anticoagulation. Careful monitoring of several coagulation components can be helpful to minimize bleeding complications, and when bleeding occurs at the site of cannula insertion, prompt surgical intervention may minimize the need to interrupt anticoagulation. Transfusion of blood products, PCCs, and fibrinogen may be considered, depending on the clinical situation.

As in any critically ill patient population, infection remains a constant concern because of the presence of intravascular devices, prolonged nature of mechanical ventilation, and compromise to the immune system that may occur in patients with severe multiorgan dysfunction. In addition, because of the emergency nature of ECMO insertion, which is often conducted at the bedside outside the sterile confines of the operating room, patients may risk inoculation with pathogenic microorganisms present in the health care setting. Because device support can last several days or weeks, many clinicians may use antibiotics for prophylaxis for a limited duration after inserting ECMO or for the duration of support. Evidence of these practices is very limited, and overuse of antimicrobial agents may add a risk of the patient developing multidrug-resistant pathogens, *Clostridium difficile* superinfection, or other adverse effects of antimicrobial agents, making this a practice that should be used cautiously. Lower respiratory tract and bloodstream infections are the most commonly encountered types of infections in this population (Haneke 2016; Burket 1999). Authors of a recent systematic review of prophylactic antibiotics in patients receiving ECMO

therapy concluded that there is no clear evidence supporting use (O'Horo 2016). However, in select patients, including those with open chests after cardiac surgery, extended antimicrobial prophylaxis can be considered.

Anticoagulation During ECMO Support

Unfractionated heparin is the most widely used anticoagulant for patients receiving ECMO support because it has a relatively short half-life and it is readily reversible and easily titrated to achieve a patient-specific level of anticoagulation (ELSO 2013). However, much debate remains regarding the most appropriate intensity of anticoagulation of patients receiving ECMO support, as well as the most effective method of monitoring this therapy (ELSO 2013). It is common practice to include several coagulation tests to monitor anticoagulation, which are combined with the patient's clinical condition (e.g., the presence of bleeding or clinical thrombosis) to guide anticoagulation decision-making. For patients with the suggestion of heparin-induced thrombocytopenia, the direct thrombin inhibitor bivalirudin or argatroban should be considered. Dose selection of the direct thrombin inhibitor should factor in existing coagulopathy and end-organ function because both agents demonstrated therapeutic levels of anticoagulation at much lower than standard doses in hemodynamically unstable patients requiring ECMO support (Ranucci 2011; Beiderlinden 2007).

Activated clotting time (ACT) and activated PTT (aPTT) are the most common coagulation tests used to monitor UFH dosing in patients receiving ECMO support. Because of the familiarity of aPTT in the ICU, many centers consider this the preferred test. However, discordance between the aPTT and the ACT has been described in the neonatal ECMO population (Khaja 2010). Furthermore, a separate analysis showed the aPTT to have a better correlation with UFH dosing than the ACT in adult patients receiving ECMO (Atallah 2014). Given these findings, it remains unclear which of the two tests is superior for monitoring anticoagulation in patients receiving ECMO support.

In a recent survey of anticoagulation practices for ECMO centers, the reported average minimum targeted ACT value was 183 seconds, and the average maximum ACT was 210 seconds (Bembea 2013). Goal therapeutic ranges for aPTT should be made laboratory-specific, according to the individual laboratory assays performed, typically targeting standard ranges of 1.5–2.5 times that of baseline. Anti-factor Xa (anti-Xa) assessment may be used at capable centers, though it is unclear at this time whether UFH anti-Xa is a safer or more effective monitoring strategy. The target anti-Xa range most commonly used is 0.3–0.7 IU/mL (Bembea 2013), though a lower goal of 0.2–0.4 may be considered in patients with a high bleeding risk. Regrettably, a poor correlation between anti-Xa and ACT has been described (Khaja 2010). The relationship between aPTT and anti-Xa is thought to be discordant because of many additional factors that

may prolong the aPTT outside UFH dosing (Vandiver 2012). Because of the variability between tests, many clinicians manage UFH by incorporating several clinical factors in addition to the coagulation tests described.

Thromboelastography (TEG) may also be used to obtain a more complete sense of a patient's global risk of coagulation and bleeding, with the added value of aiding the clinician in determining the need for transfusion or antifibrinolytic therapy. Reviews of TEG are available elsewhere for clinical pharmacists unfamiliar with this test (Salooja 2001; Mallett 1992). The TEG also aids in determining the presence of UFH anticoagulant effects when a standard TEG R-time is compared with the R-time of a TEG evaluated in the presence of heparinase (Salooja 2001). This may aid the clinician in determining whether the prolongation of aPTT and other coagulation times is attributable to heparin effects or some other coagulopathy associated with organ dysfunction, previous use of oral anticoagulants, or factor deficiency, which may all be encountered in the patient with cardiogenic shock.

Fibrinogen replacement may be indicated if a patient develops a coagulopathy or disseminated intravascular coagulation. If fibrinogen is below critical concentrations (100 mg/dL), cryoprecipitate supplementation may enhance the safety of therapeutic anticoagulation and minimize any risk of spontaneous life-threatening hemorrhage (Levy 2014). Some centers incorporate antithrombin III (AT III) monitoring and supplementation in AT III-deficient patients to avoid heparin resistance and ensure adequate anticoagulation. In an analysis of the efficacy of AT III supplementation, there was no discernible effect on heparin dosing, although anti-Xa concentrations were greater in those receiving AT III replacement. There was no observed benefit on the need for circuit exchange or overall heparin dosing in this analysis (Byrnes 2014). Within the ELSO guidelines, AT III replacement remains a consideration in acquired AT III deficiency in the presence of excessive heparin dosing (greater than 35 units/kg/hour) and/or an AT III activity level less than 30% (ELSO 2013).

Impact of ECMO on Pharmacokinetics and Pharmacodynamics

A significant value of clinical pharmacists to the multidisciplinary team is their unique understanding, appreciation, and perspective for therapeutic drug monitoring. In some cases, this represents monitoring drug concentrations for traditional medications; however, with the introduction of an ECMO circuit, additional influences to drug disposition may occur beyond the traditional factors that affect volume of distribution and clearance. During ECMO initiation, there is a significant addition to plasma volume, which will immediately affect volume of distribution (Shekar 2012a; Mehta 2007). This initiation (cannulation) process can add volume to the patient's systemic circulation using crystalloids, colloids, or blood products as priming solutions for the circuit,

which would be expected to dilute drug concentrations during ECMO initiation. In addition, many drugs are well known to adhere to artificial surfaces and hence may become sequestered within the oxygenator or other components of the ECMO circuit. This drug loss may be greater during earlier phases of ECMO support, and lipophilic drugs may be more prone to loss within the circuit. Although hydrophilic drugs are less affected by drug loss, they are still likely to have a greater volume of distribution because of the added plasma volume within the circuit. Drugs that have had significant loss within ECMO circuits compared with control conditions include fentanyl, midazolam, propofol, heparin, and voriconazole, potentially warranting different management strategies for each to ensure that therapeutic doses are maintained (Shekar 2012b; Mehta 2007).

Sedation and Analgesia

Optimizing sedation and analgesia can be one of the greater challenges in patients undergoing ECMO support. Often, patients with refractory respiratory failure may require excessive doses of analgesic and sedative agents. Because oxygen consumption can be increased in agitated patients, poor sedation and persistent agitation may not only cause tissue hypoxia, but may also increase the likelihood that patients harm themselves by dislodging ECMO cannulas, endotracheal tubes, nasogastric tubes, and intravascular catheters. Several reports have shown significant sedative or analgesic drug loss within ECMO circuits, including midazolam, propofol, dexmedetomidine, and fentanyl. This phenomenon may warrant greater doses, especially early in ECMO support, as the presence of the ECMO circuit may mimic the drug pharmacokinetics in a multicompartment model (Wagner 2012; Mehta 2007; Mulla 2000).

Morphine or hydromorphone may serve as a useful analgesic alternative to fentanyl in patients with uncontrolled pain receiving ECMO because both agents are more hydrophilic than fentanyl (Shekar 2012b). Lorazepam may be a less lipophilic benzodiazepine option than midazolam or diazepam, but despite such has demonstrated some degradation compared with control concentrations in an in vitro model (Mulla 2000). In addition, as might be expected with any multicompartment pharmacokinetics, a period of drug redistribution may persist after discontinuation, possibly causing a prolonged sedative effect. Many centers maintain patients awake and, in some cases, non-mechanically ventilated, to encourage mobility, minimizing the risk of over sedation and mechanical ventilation complications.

Antibiotic Therapy

In patients undergoing ECMO support, infection is very common and multifactorial. Development of infection while the patient is receiving ECMO is a constant concern that should be met with rapid collection of blood, urine, and respiratory tract cultures, as well as initiation of empiric broad-spectrum

antimicrobial agents according to patient risk factors and local antimicrobial resistance patterns.

With any antimicrobial agent selected, loading doses should be given with consideration of the greater volume of distribution present with the ECMO circuit. This is especially important to achieve effective therapeutic concentrations initially in a patient who may be experiencing septic shock. As with the sedative medications, a component of drug sequestration of antimicrobial agents may be within the circuit and this poses the risk of treatment failure because of ineffective drug concentrations (Shekar 2012b). Antimicrobial agents that are very lipophilic should be avoided, if possible. When therapeutic drug monitoring is feasible (e.g., vancomycin, aminoglycosides), drug concentrations should be monitored often. Most β -lactams are hydrophilic, and cefotaxime, meropenem, and piperacillin/tazobactam are minimally affected by the presence of ECMO; therefore, clinicians can follow conventional dosing for these medications according to the patient's CrCl (Donadello 2015; Ahsman 2010).

In fungal infections, amphotericin B and hydrophilic azole antifungals may be the agents of choice to sustain effective antifungal concentrations, depending on resistance patterns (Watt 2012; Ruiz 2009). Echinocandins have inconsistent pharmacokinetics with ECMO, and voriconazole, a lipophilic azole antifungal, consistently undergoes significant drug loss within the ECMO circuit (Ruiz 2009; Spriet 2009). Finally, in influenza infection, higher doses of the antiviral neuraminidase inhibitor oseltamivir (150 mg twice daily) have been described in patients receiving ECMO, in whom lower drug concentrations were reported than in patients not receiving ECMO (Eyler 2012). This report differed somewhat from a later study describing no difference in oseltamivir concentrations between patients receiving ECMO and patients who were not (Mulla 2013). Nonetheless, oseltamivir concentrations at standard doses were considered sufficient by both groups of investigators to achieve effective concentrations in treating severe influenza infections; therefore, a higher dosing strategy may not be necessary to provide therapeutic concentrations (Mulla 2013; Eyler 2012).

PERCUTANEOUS LVADS

Indications for and Types of pVADs

The main indications for percutaneous left ventricular assist device (pVAD) therapy are for hemodynamic support during high-risk percutaneous coronary intervention and in refractory cardiogenic shock caused by acute myocardial infarction or severe HF. Currently, two FDA-approved devices may be used in these clinical settings. The first is the Impella series (Abiomed, Danvers, MA), which includes the Impella 2.5, the 5.0, the CP (Cardiac Power), and the RP. The Impella 2.5 is a catheter-mounted micro-axial pump mounted on a 9-French catheter shaft, which houses the motor driveline and the purge line system. Insertion is usually achieved through a femoral

approach, and the pump is positioned across the aortic valve into the LV under fluoroscopy (Sjauw 2009). Expelling aspirated blood from the LV into the ascending aorta, the Impella 2.5 at its maximal rotation speed of 51,000 rpm can provide flow up to 2.5 L/minute. The Impella CP uses the same platform as the 2.5 device, but it can provide additional cardiac support and operates with a mean flow of 3–4 L/minute. The Impella 5.0 device carries a larger motor capable of providing up to 5 L/minute of support; as such, it is inserted into the LV by femoral cutdown or through the axillary artery. Finally, the Impella RP is approved to provide circulatory support to those who develop acute right HF; this pump delivers blood from an inlet area in the inferior vena cava through the cannula to the outlet opening near the tip of the catheter in the pulmonary artery.

The TandemHeart pVAD (CardiacAssist, Pittsburgh, PA) is a low-speed centrifugal continuous-flow pump that can be introduced percutaneously in the cardiac catheterization laboratory (Thiele 2001). Inserted by a venous trans-septal puncture through the femoral vein, a 21-French left atrial cannula channels blood into the pump, and a 15- to 17-French femoral artery cannula carries the blood to the systemic arterial circulation. The TandemHeart is capable of up to 4.1 L/minute of assisted cardiac output and can be used for both left- and right-sided mechanical support.

Hemodynamic Consequences of pVADs

The Impella devices propel blood from the LV into the ascending aorta, thereby unloading the LV and increasing cardiac output. They reduce myocardial oxygen consumption, improve MAP, and reduce PCWP (Rihal 2015). The Impella 2.5 provides a greater increase in cardiac output than an IABP, but less than the TandemHeart device (Table 2-2). The more powerful Impella CP and 5.0 devices are comparable with the TandemHeart device in MCS. Similar to the TandemHeart, adequate RV function is necessary to maintain LV preload and hemodynamic support during biventricular failure.

During MCS with the TandemHeart, both the LV and the device contribute flow to the aorta simultaneously (thereby working in parallel, or tandem, rather than in series). The redirection of blood from the LA reduces LV preload, LV workload, filling pressures, wall stress, and myocardial oxygen demand (see Table 2-2) (Rihal 2015). The increase in arterial blood pressure and cardiac output supports systemic perfusion. The aorta is thus perfused and pressured by both the LV and the TandemHeart, with the relative contribution of each varying and dependent on LV response to the device. Not uncommonly, LV contraction virtually ceases, and perfusion is pump-dependent with a flat MAP curve. Like the Impella devices, ventricular tachycardia or fibrillation usually (but not always) renders the TandemHeart ineffective because of RV failure.

Anticoagulation During pVAD Support

Successful use of Impella devices is predicated on effective heparin-based anticoagulation. The manufacturer recommends

Table 2-2. Comparison of Available Temporary Support Devices

	IABP	Impella	TandemHeart	VA ECMO
Maximum support	0.5–1 L/min	2.5, 3.5, or 5.0 L/min	Up to 4.1 L/min	> 5 L/min
LV unloading	+	++,+++,++++	+++	++
Coronary perfusion	+	+	–	–
Bleeding risk	+	++	+++	++++
Management complexity	+	++	++++	+++
Maximum implant time ^a	Weeks	7 days	14 days	Days to weeks

^aAccording to manufacturer recommendations.

LV = left ventricular; VA ECMO = venoarterial extra corporeal membrane oxygenation.

administering UFH through a purge solution, which is used to lubricate the motor and maintain a pressure within the device at 300–1100 mm Hg. Historically, the default purge solution is 25,000 units of UFH in 500 mL of 20% dextrose solution (50 units/mL), though lower concentrations of UFH (e.g., 25 units/mL) can be used.

Recently, the device manufacturer changed the recommended default dextrose concentration to 5%, which is relevant because this reduction in the viscosity of the purge solution will likely increase the flow rate (and thus the UFH exposure) by as much as 30%–40%. The device console automatically adjusts the flow rate of the purge to 2–30 mL/hour to maintain purge pressure, which is problematic because such fluctuations can significantly alter the amount of UFH exposure to the patient. Adding to this already complicated scenario is the need to maintain therapeutic anticoagulation (ACT of 160–180 seconds or aPTT of 60–80 seconds), which often necessitates supplemental intravenous UFH (Seyfarth 2008). The simultaneous administration of UFH in the purge solution (which is controlled by the console) together with intravenous UFH poses a significant hazard for medication error and heparin over- or underdosage. The Patient Care Scenario highlights this problem and offers potential solutions to avoid harm and optimize anticoagulation strategies in these complicated patients.

Similar to the Impella devices, anticoagulation with the TandemHeart is complicated by the need for a heparinized infusate of 1000 mL of normal saline with 90,000 units of UFH. This infusate runs at a fixed rate of 10 mL/hour, which, unlike the Impella devices, will not fluctuate UFH exposure. It is important to highlight that the infusate must be saline because dextrose-containing products could damage the motor and lead to catastrophic failure of the device. Additional UFH can be administered intravenously as needed to achieve therapeutic anticoagulation (Table 2-3).

Complications of pVAD Therapy

The most commonly reported complications of Impella placement are limb ischemia, vascular injury, and bleeding requiring blood transfusion. Vascular complications common to all transfemoral procedures such as hematoma, pseudoaneurysm, and arteriovenous fistula and retroperitoneal hemorrhage can occur with any mechanical support device. Hemolysis because of mechanical erythrocyte shearing has

Table 2-3. Example Anticoagulation Protocol for the TandemHeart Device

Initiating Anticoagulation

aPTT (seconds)	Instructions
< 55	Continue current infusate (heparin 45,000 units/500 mL saline) at 10 mL/hr, and initiate intravenous heparin 2 units/kg/hr
55–75	Therapeutic – No changes
76–90	Change infusate to heparin 25,000 units/500 mL saline at 10 mL/hr, and initiate intravenous heparin at 2 units/kg/hr
91–110	Change infusate to heparin 25,000 units/500 mL saline at 10 mL/hr; do not initiate intravenous heparin
> 110	Change infusate to saline (no heparin) at 10 mL/hr

Information from: Lee Y, Weeks PA. Effectiveness of protocol guided heparin anticoagulation in patients with the TandemHeart percutaneous ventricular assist device. *ASAIO J* 2015;61:207-8.

Patient Care Scenario

PART 1

A woman (weight 75 kg) is admitted to the ICU with an Impella CP device in place. Her purge solution (25,000 units/500 mL of dextrose 5%) is currently running at 10 mL/hour, or 500 units/hour of heparin. According to the heparin protocol for this hospital, her total hourly heparin dose should be 900 units (75 kg × 12 units/kg) to achieve an aPTT of 60–80 seconds. According to this protocol, how much intravenous heparin should the patient receive?

ANSWER

The patient should be initiated on an intravenous heparin drip at a rate of 400 units/hour to equal a total hourly dose of 900 units/hour (500 units/hour from the purge plus 400 units/hour intravenously).

PART 2

Two hours after initiating intravenous heparin, the nurse notices that the Impella controller has reduced the flow rate of the purge solution to 8 mL/hour, or 400 units/hour of heparin. She notifies the physician, who asks the ICU pharmacist for assistance. What is the most appropriate action to take at this time?

ANSWER

The pharmacist will recommend to increase the rate of the intravenous heparin by 100 units/hour to 500 units/hour so that the patient continues to receive a total hourly dose of 900 units/hour (400 units/hour from the purge plus 500 units/hour intravenously).

PART 3

After 6 hours of support, the first aPTT value is 47 seconds (goal 60–80 seconds). The ICU team asks the pharmacist for assistance with anticoagulation management. What is the most appropriate action at this time?

ANSWER

Because the aPTT is subtherapeutic, the patient will require more heparin. This can be accomplished by increasing the intravenous heparin. Remember that the purge flow rate is controlled by the device and cannot be titrated to achieve a therapeutic aPTT. A reasonable solution would be to increase the infusion rate for the intravenous heparin by 100 units/hour, making the new total hourly dose 1000 units/hour (400 units/hour from the purge plus 600 units/hour intravenously).

1. Jennings DL, Nemerovski CW, Kalus JS. Effective anticoagulation for a percutaneous ventricular assist device using a heparin-based purge solution. *Ann Pharmacother* 2013;47:1364-7.

been reported within the first 24 hours of use in 5%–10% of patients; these patients may respond to device repositioning (Lauten 2013). Persistent hemolysis is an indication for device removal. As the Impella device traverses the aortic valve and sits in the LV, its use is contraindicated in patients with a mechanical aortic valve, or in those with an LV

thrombus. Aortic stenosis and regurgitation are relative contraindications, though reports exist of hemodynamic rescue in critical aortic stenosis or in facilitating valvuloplasty. These devices should not be placed in patients with severe peripheral arterial disease or in those who cannot tolerate systemic anticoagulation. Finally, use of Impella theoretically worsens right-to-left shunting and hypoxemia in patients with a preexisting ventricular septal defect.

Because the TandemHeart does not pass through the aorta, it can safely be used in patients with aortic valvular pathology. The trans-septal puncture needed to implant the device exposes patients to unique complications, like cardiac tamponade. Other possible complications include thrombosis, air embolism, and hemolysis. Care must be taken to prevent dislodgement of the left atrial cannula, particularly during patient transport or if patients move their leg, because dislodgement into the right atrium will result in massive right-to-left shunt and severe systemic oxygen desaturation. The cannula could also migrate into a pulmonary vein, which would lead to device malfunction.

DURABLE LVAD THERAPY

Indications for and Types of Durable LVAD Pumps

Current guidelines for HF management suggest that durable LVAD therapy can be considered to prolong survival for carefully selected patients (see Table 2-1) with stage D disease (Yancy 2013). These devices can be used either as a bridge-to-transplantation or as destination therapy in those who are not candidates for heart transplantation. Both of the commercially available devices in the United States operate under continuous flow (CF-LVAD). The HeartMate II (Thoratec, Pleasanton, CA) operates by a fully levitated internal impeller (similar to an Archimedes screw) and delivers up to 10 L/minute of cardiac output by axial laminar flow. The HeartWare HVAD (HeartWare International, Framingham, MA) is a smaller pump that is inserted directly into the pericardium; this device uses a waterwheel-like impeller to generate full cardiac support by centrifugal flow. Both devices cannulate the apex of the LV to provide direct mechanical cardiac unloading, and each propels blood forward through an outflow graft anastomosis to the ascending aorta. The HeartMate II (and the investigational HeartMate III) devices provide a snapshot of four device parameters (flow, speed, pulsatility index, and power) on the device counsel, whereas the HeartWare HVAD monitor provides continuous waveform analysis of flow and power (Table 2-4).

Hemodynamic Consequences of Durable LVADs

Continuous pumping of blood directly from the LV independently of the cardiac cycle results in loss of the normal isovolumic periods. Unlike other forms of support such as the Impella devices, removal of blood from the LV does not

Table 2-4. Device Parameters for CF-LVADs

Parameter	Normal Values	Can Be Elevated by	Can Be Decreased by	Pharmacotherapy Considerations
Flow	4–6 L/min ^a	<ul style="list-style-type: none"> • Sepsis • Device thrombosis • Aortic insufficiency 	<ul style="list-style-type: none"> • RV failure • Dehydration • Hemorrhage • Hypertension • Arrhythmias 	<ul style="list-style-type: none"> • Monitor for decreases in flow when titrating β-blockers or diuretics • Titrate afterload-reducing agents to avoid hypertension and optimize flow • Monitor for evidence of blood loss or device thrombosis
Speed	8800–9800 rpm ^b 2800–3400 rpm ^c	<ul style="list-style-type: none"> • None—adjusted by health care team 	<ul style="list-style-type: none"> • Dehydration 	<ul style="list-style-type: none"> • Sudden drops in speed (i.e., suction event) may suggest dehydration and should prompt assessment of diuretic regimen, fluid status, and potential hemorrhage
Pulsatility index	4–7 ^d	<ul style="list-style-type: none"> • Hypertension 	<ul style="list-style-type: none"> • Hypotension • Dehydration • RV failure 	<ul style="list-style-type: none"> • Sudden drops in pulsatility index (i.e., suction event) in HeartMate II may suggest dehydration and should prompt assessment of diuretic regimen and fluid status
Power	5–7 W	<ul style="list-style-type: none"> • Device thrombosis • Hypertension 	<ul style="list-style-type: none"> • Hypotension • Sepsis 	<ul style="list-style-type: none"> • Sustained power elevation should prompt evaluation for device thrombosis

^aNormal value depends on the patient's BMI.

^bTypical range for HeartMate II device.

^cTypical range for HeartWare HVAD.

^dCalculated only by HeartMate II device; indirectly measures degree of device support and volume status.

CF = continuous flow; RV = right ventricular.

Information from: Jennings DL, Schillig J, Chambers R. The pharmacotherapy of the HeartMate II, a continuous flow left-ventricular assist device, in patients with advanced heart failure: integration of disease, device and drug. *Ann Pharmacother* 2010;44:1647-50.

depend on ejection through the aortic valve. As pump flow rate increases, the LV becomes increasingly unloaded, peak LV pressure generation decreases, and there are marked decreases in myocardial oxygen consumption. At the same time, arterial blood pressure increases such that peak LV pressure and arterial pressure are increasingly dissociated. This direct unloading also results in decreased left atrial and PCWP. Over time, these improvements in blood oxygenation, systemic pressures, and perfusion may reverse the metabolic milieu of end-stage HF and invoke beneficial secondary changes in LV contractility and peripheral resistance.

Management of Hypertension

All CF-LVADs are sensitive to increases in afterload such that elevations in systemic arterial pressure can impede device function and reduce forward flow (see Table 2-4). The presence of hypertension also presages a heightened risk of stroke in CF-LVAD recipients (Nassif 2015). Depending on the device speed and the residual native left-heart function, these patients will lack pulsatility; thus, blood pressure targets will be based on the MAP. Although most ICU patients have arterial line access for monitoring, noninvasive blood pressure monitoring may be performed with a Doppler probe given the aforementioned loss in pulsatility.

Clinical pharmacists facing systemic arterial hypertension (usually defined as a MAP greater than 90 mm Hg) should first assess systemic perfusion and begin to withdraw inotropic support in patients with adequate mixed venous oxygen saturation (SvO_2) and stable end-organ function. If hypertension persists, or if these drugs cannot be weaned because of low SvO_2 (e.g., less than 65%), a systemic vasodilator should be initiated. If intravenous therapy is needed, nicardipine is often the first drug of choice because of its relatively neutral effects on cardiac inotropy and chronotropy, though sodium nitroprusside can be considered as an alternative agent. Patients should be transitioned to oral therapy as soon as possible; ACE inhibitors are considered first-line therapy in those with stable renal function and acceptable serum potassium levels (Lampert 2014). Dihydropyridine calcium channel blockers (e.g., amlodipine) are also acceptable options, as are β -receptor antagonists (assuming that RV function is adequate). Most patients with CF-LVADs generally require one or two antihypertensive medications to maintain an optimal MAP (less than 80 mm Hg).

Management of Ventricular Arrhythmias

Sustained ventricular arrhythmia can occur in up to 40% of CF-LVAD recipients, and it occurs most commonly in patients with a history of this condition (Raasch 2012). As the LV is completely unloaded, the pathophysiologic sequela of these arrhythmias may be negligible. There have been reports of patients surviving hours and, in extreme cases, months of ventricular fibrillation. However, the loss of organized contraction from the unsupported RV can lead to hemodynamic destabilization in select patients by reducing pump flow secondary to unsatisfactory left-sided volume for ventricular filling (see Table 2-4). Therefore, treatment decisions regarding ventricular arrhythmias should be made on a case-by-case basis according to the patient's overall condition. Although asymptomatic arrhythmias may not require intervention, those associated with hypotension, RV failure, or clinical symptoms (e.g., dizziness or palpitations) warrant treatment.

Amiodarone remains the preferred antiarrhythmic agent for patients with a CF-LVAD. In addition to the customary monitoring for this agent, clinical pharmacists should remember that initiating amiodarone therapy may alter the pharmacodynamic response to warfarin, which is germane because virtually all patients with durable CF-LVADs require oral anticoagulation (Edwin 2010). For patients whose amiodarone therapy fails or who develop intolerance to this agent, lidocaine is an appropriate secondary treatment option. β -Blockers are very effective antiarrhythmic medications and should also be initiated whenever possible in patients with CF-LVADs; however, the potential for negative inotropy and RV dysfunction may limit their use (Refaat 2008). Therefore, clinical pharmacists should closely monitor these patients for signs of RV failure (see the text that follows) when initiating or titrating β -Blockers.

Management of RV Failure

The anatomy and physiology of the RV are very distinct from that of the LV. Although the LV has three muscle layers (oblique, circular, and longitudinal), the RV has only two (circumferential and longitudinal) (Sheehan 2008). Furthermore, although the LV exerts powerful torsional and rotational forces, the RV operates using peristaltic contractions (similar to the GI smooth muscles). The RV largely depends on the low hydraulic impedance characteristics of the pulmonary vascular bed and, as such, can achieve comparable output with a myocardial energy cost of about one-fifth that of the LV.

Unanticipated RV failure occurs in up to 40% of durable CF-LVAD recipients and is associated with significantly worsened survival (Tsiouris 2015). No uniform definition for severe RV failure exists; however, this pathology is commonly described as the need for placing an RV assist device or using intravenous inotropes for more than 14 days postoperatively. The many preoperative risk factors for developing RV failure include elevations in central venous pressure, diminished RV stroke work index and RV contractility on echocardiography, and the presence of signs and symptoms suggestive of right HF (Morgan 2013).

Right ventricular failure in the ICU setting commonly manifests as a constellation of hypotension, low device flow and low pulsatility indices, and echocardiographic evidence of RV dysfunction (see Table 2-4). Distinguishing RV failure from other causes of hypotension and low flow (e.g., inadequate device speed or hypovolemia) can be difficult, and continuous pulmonary artery catheter monitoring during pump speed optimization are often necessary to confirm the diagnosis (Figure 2-2).

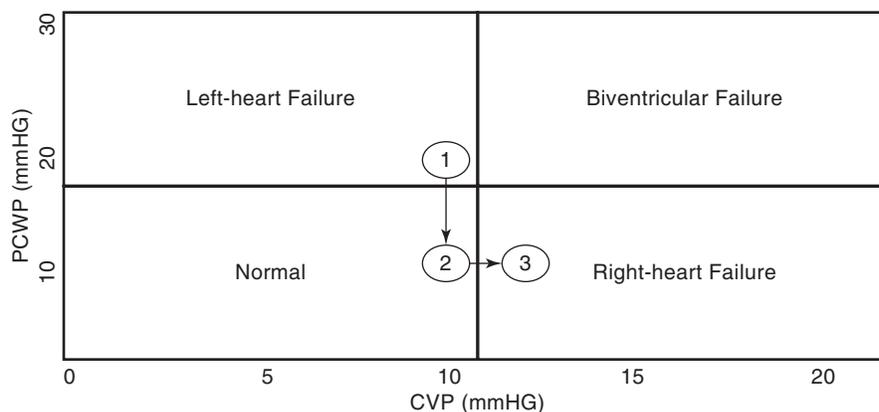


Figure 2-2. Use of continuous pulmonary artery catheter monitoring to confirm RV failure. Central venous pressure (CVP) is plotted on the x-axis against pulmonary capillary wedge pressure (PCWP) on the y-axis. Patients with elevations in both of these values likely have biventricular failure, while isolated elevations in either CVP or PCWP may represent either right- or left-heart failure, respectively. Point 1 represents a low speed which is not adequate to unload the left-ventricle. At point 2, the speed has been optimized, and both ventricles are adequately decompressed. At point 3, the speed has been increased too much, resulting in a leftward shift of the intraventricular septum and subsequent right-ventricular failure.

Although a high PCWP can be managed by increasing the device speed, isolated elevations in CVP (which suggests RV failure) usually require pharmacologic intervention. As mentioned previously, the RV normally exists in a low-pressure environment, and thus even mild elevations in afterload (i.e. high pulmonary vascular resistance [PVR] values) can drastically impair systolic function. This notion was reinforced by recently published data that demonstrated the RV is more sensitive to even small increases in afterload pressure early after CF-LVAD implantation (Houston 2016). Therefore the choice of agent for pharmacologic support of the failing RV hinges on the patient's PVR value (Figure 2-3).

In the setting of RV failure with normal PVR values, traditional inotropic therapy (i.e., dobutamine or milrinone) should be sufficient to improve contractility and RV output. Conversely, if the PVR is elevated (greater than 250 dynes/sec/cm⁵ or 3 Wood units), or the patient has other evidence of a high RV afterload (such as a transpulmonary gradient greater than 12 mm Hg [mPAP-PCWP]), then a selective pulmonary artery vasodilator would be the preferred initial

pharmacologic agent. A complete review of these agents is beyond the scope of this chapter; however, Table 2-5 describes the drugs commonly used in the ICU setting for acute RV failure.

Inhaled nitric oxide (iNO) is historically the most commonly used treatment option, however the high cost represents a significant limitation for this therapy. Inhaled epoprostenol is significantly less expensive than iNO, but it is cumbersome to administer and can increase bleeding risk through inhibition of platelet aggregation (Groves 2014). Recent pilot data suggest that inhaled milrinone can also be used for acute RV failure after CF-LVAD implantation; however, absorption from the pulmonary circulation produces therapeutic plasma milrinone levels, and hence patients receiving this modality may be at risk for hypotension and cardiac arrhythmias (Haglund 2015). In cases of severe, refractory post-operative pulmonary artery hypertension, combining inhaled pulmonary vasodilators with complimentary pharmacology (e.g., epoprostenol + milrinone or iNO + iloprost) can be considered as salvage therapy (Antoniou 2013 and Haraldsson 2011). If pharmacologic

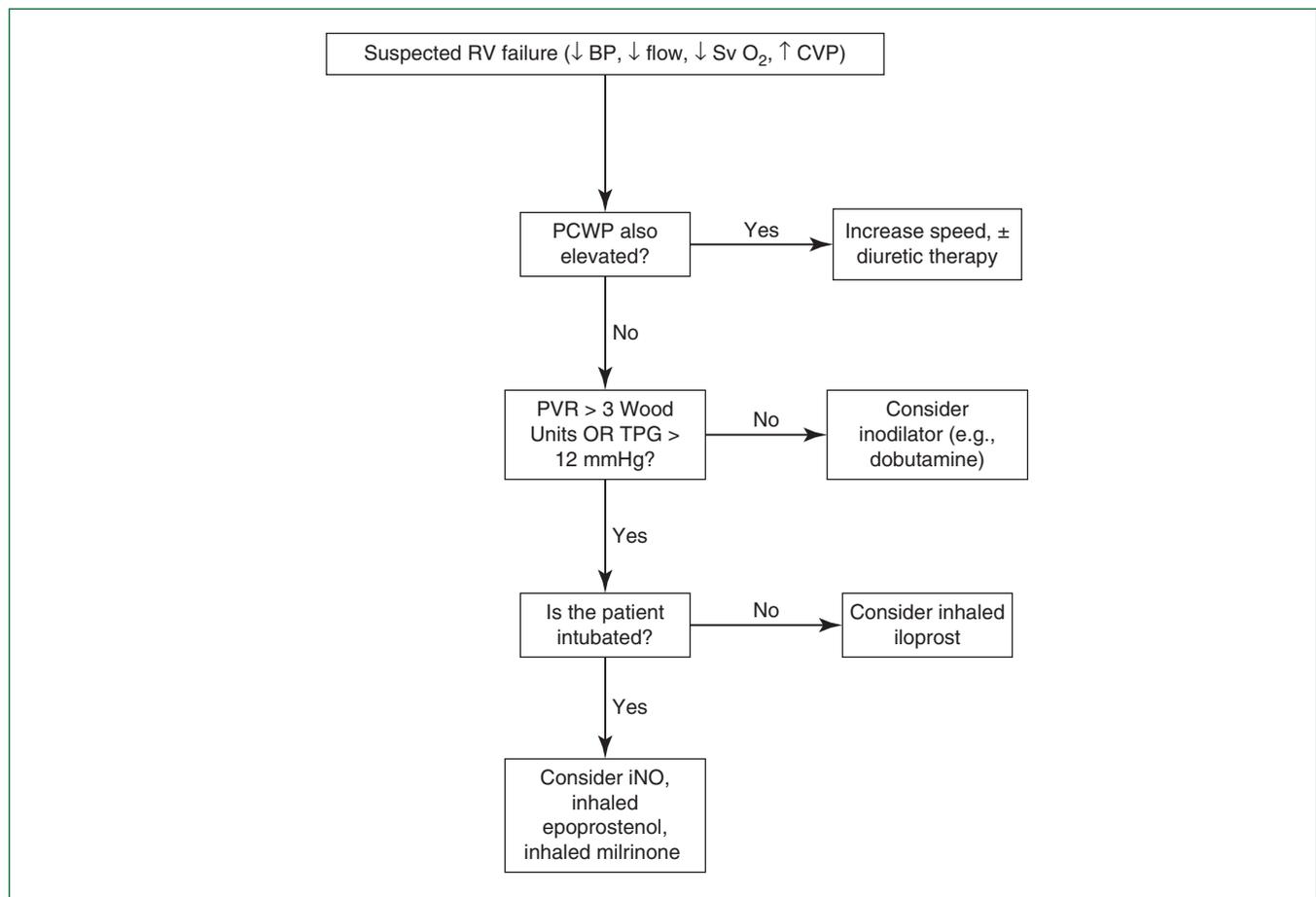


Figure 2-3. Flow chart for pharmacologic management of right-ventricular (RV) failure.

BP = blood pressure; CVP = central venous pressure; iNO = inhaled nitric oxide; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; Sv O₂ = mixed venous oxygen saturation; TPG = transpulmonary gradient.

Table 2-5. Comparison of Selective Pulmonary Artery Vasodilators Commonly Used in the ICU

Agent	Mechanism of Action	Common Doses	Notes
Inhaled nitric oxide	Activates intracellular guanylyl cyclase, which increases concentrations of cyclic guanosine 3'5'-monophosphate	1–20 ppm by continuous inhalation	<ul style="list-style-type: none"> • Very short half-life • Can cause methemoglobinemia • Very expensive • Limited systemic exposure
Inhaled epoprostenol	Activates intracellular adenylate cyclase, which increases concentrations of cyclic adenosine monophosphate	25–50 ng/kg/min	<ul style="list-style-type: none"> • Complicated administration • Patient must be intubated • Less expensive • Some systemic exposure <ul style="list-style-type: none"> ◦ Potential for platelet inhibition and bleeding ◦ Potential hypotension
Iloprost	Activates intracellular adenylate cyclase, which increases concentrations of cyclic adenosine monophosphate	2.5–5 mcg inhaled six to nine times daily	<ul style="list-style-type: none"> • Ease of administration • Patient can be extubated • Very expensive • Some systemic exposure <ul style="list-style-type: none"> ◦ Potential for platelet inhibition and bleeding ◦ Potential hypotension
Inhaled milrinone	Inhibits phosphodiesterase type 3, which increases concentrations of cyclic adenosine monophosphate	6 mg/hr continuous inhalation	<ul style="list-style-type: none"> • Complicated administration • Patient must be intubated • Less expensive • Systemic exposure <ul style="list-style-type: none"> ◦ Potential hypotension ◦ Arrhythmia

efforts to reverse RV failure are unsuccessful, then mechanical right heart support should be instituted. Unfortunately, need for a RV assist device after CF-LVAD implantation is associated with a high post-operative mortality (Morgan 2013).

Thromboprophylaxis During LVAD Support

All commercially available durable CF-LVADs carry a risk of thrombosis, which can include clotting within the device itself (i.e., pump thrombus) as well as ischemic stroke caused by device-related emboli. Lifelong combination therapy with warfarin-based anticoagulation and antiplatelet agents is required to mitigate these devastating complications. No randomized data exist comparing antithrombotic regimens in CF-LVAD recipients; as such, significant heterogeneity exists within the field, and practice is often guided by local center experience (Jennings 2016b). For both the HeartMate II and the HeartWare HVAD, intravenous UFH should be initiated as soon as surgical hemostasis has been achieved. Both device manufacturers recommend targeting a lower aPTT for the first 24–48 hours (e.g., 45–50 seconds), with the eventual goal of titrating toward a value of 55–65 seconds. Aspirin should also be initiated by postoperative day 2 at a dose of 81 mg daily for the HeartMate II and a dose of 162–325 mg daily for the HeartWare HVAD. For the HeartMate II device,

some centers still use dual antiplatelet therapy with aspirin and dipyridamole, whereas other centers (particularly in Europe) omit antiplatelet agents entirely (Jennings 2016b).

When transitioning from UFH to warfarin, the ICU clinical pharmacist should assist with dosing, particularly when major drug-drug interactions are present. If the patient was taking warfarin before CF-LVAD implantation, historical requirements can be used as a basis for postoperative dosing (Jennings 2012). Warfarin genotype data, if available, can also be helpful in selecting an appropriate initial dosing regimen (Jennings 2016a). The pharmacist should ensure that UFH is continued until at least five doses of warfarin have been administered and until the INR is therapeutic for at least two readings taken 24 hours apart (Colombo 2016).

Both the HeartMate II and the HeartWare HVAD manufacturers advocate for an INR target of 2–3; however, many centers use narrower ranges (e.g., 2–2.5 or 2.5–3) (Jennings 2016b). Although there are no randomized data comparing one INR target range against another, use of narrower targets is generally associated with lower time within the therapeutic range and poorer anticoagulation quality (Kuyumjian 2016). In light of this, we recommend a standard initial INR range of 2–3 for all durable CF-LVAD recipients. This recommendation is further supported by a recent analysis

that assessed over 10,000 INR values in 249 patients with CF-LVADs and found that the optimal INR, according to the weighted mortality of thrombotic and bleeding events, was 2.6, with low rates of adverse events falling in INR values 2.0–3.2 (Nassif 2016).

Infectious Complications of Durable LVAD Therapy

Infection is a major complication associated with LVAD therapy, with reported rates of 25%–80% (Nienaber 2013). The clinical spectrum of infection in CF-LVAD recipients includes those related to the device (e.g., the percutaneous driveline) as well as non-LVAD-related infections (e.g., pneumonia, bacteremia). Although chronic infection of the driveline is the most common infection site, these patients rarely require ICU-level care for this condition (Nienaber 2013). Some patients with CF-LVADs may develop severe infections, including bacteremia and sepsis. When faced with severe infection and critical illness, the clinical pharmacist must be familiar with the epidemiology of CF-LVAD infections as well as the potential for altered pharmacokinetics of antimicrobial therapy in patients with durable devices.

Several studies have shown that the continuum of pathogens associated with LVAD-related infection encompasses gram-positive and gram-negative bacteria as well as fungal species. Methicillin-sensitive *Staphylococcus aureus*, coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus* sp., *Pseudomonas aeruginosa*, *Klebsiella* sp., *Escherichia coli*, *Stenotrophomonas* sp., *Serratia* sp., *Candida* sp., *Propionibacterium* sp., diphtheroids, and *Corynebacterium* sp. have all been identified in these patients (Nienaber 2013). As such, clinical pharmacists caring for CF-LVAD recipients with severe infections should institute broad-spectrum antimicrobial therapy, including agents that cover resistant bacteria (e.g., methicillin-resistant gram-positive cocci, *Pseudomonas* sp.) and *Candida* sp. Choices regarding specific agents (both antimicrobial and antifungal) should incorporate local antibiogram data and involve specialists in infectious disease as needed. Unfortunately, the optimal treatment duration for CF-LVAD-related infections remains undefined. Many patients are treated with chronic suppressive antimicrobial therapy especially in the setting of recurrent infection as is common with drive-line infection, for example.

Limited data have suggested that CF-LVAD recipients have a larger volume of distribution and a lower-than-anticipated drug clearance compared with non-LVAD recipients, even in the face of apparent euvolemia and normal hemodynamics (Jennings 2014b). Clinical pharmacists must therefore be vigilant with monitoring for both clinical efficacy and toxicity associated with antimicrobial therapy and implement therapeutic drug monitoring, whenever possible.

Bleeding Complications of Durable LVAD Therapy

Gastrointestinal bleeding, often originating from arteriovenous malformations within the small intestine and colon, affects over 15% of patients receiving durable LVAD support (Goldstein 2015). Recent evidence suggests that sustained elevations in serum thrombin concentrations during mechanical support generate an excess of angiotensin-2, which appears to drive the growth of these arteriovenous malformations (Tabit 2016). Compounding these anatomic lesions is the depletion of high-molecular-weight von Willebrand multimers from LVAD-induced shear stress, producing a physiologic state of hypocoagulability (Bartoli 2015). Although these anatomic and physiologic derangements can lead to persistent and recurrent mucosal bleeding, rarely are these types of hemorrhage life threatening. Furthermore, treatment of GI bleeding is predominantly nonpharmacologic (i.e., endoscopic intervention) (Goldstein 2015). Hence, the remainder of this section will focus on more serious types of bleeding and on the conundrum of anticoagulation reversal in patients receiving durable device support. Given the innate thrombotic nature of CF-LVADs, bleeding necessitating anticoagulation reversal is a particularly precarious clinical scenario with the potential for catastrophic complications. As such, anticoagulation reversal should be reserved for patients with a potentially life-threatening hemorrhage. Very limited data suggest that common modalities, including 3- and 4-factor PCCs, vitamin K, and fresh frozen plasma, can safely be used to reverse the effects of warfarin (Chen 2015; Jennings 2014a). According to published guidelines for anticoagulation in patients without LVADs, a regimen of a 4-factor PCC and intravenous vitamin K is the preferred warfarin reversal strategy in patients with CF-LVADs (Guyatt 2012) with a life-threatening bleed. Because of the high risk of thromboembolism associated with recombinant factor VIIa in patients with CF-LVADs, this agent should be avoided, if possible, for reversing warfarin in acute hemorrhage (Jennings 2014a).

Should the clinical pharmacist be forced to reverse anticoagulation, device settings (see Table 2-4), hemodynamic parameters (e.g., blood pressure and cardiac output), and laboratory measurements of hemolysis (e.g., serum lactate dehydrogenase and plasma free hemoglobin) should all be diligently monitored for signs of pump thrombosis (see the discussion in the text that follows on thrombotic complications). Recent literature suggests that acute hemorrhage and the ensuing interruption in anticoagulation is a risk factor for subsequent thrombotic complications (Stulak 2014). Therefore, once hemostasis has been achieved and the patient is clinically stable, anticoagulation should usually be reinitiated carefully with UFH. Warfarin should only be reinitiated after the patient has remained free of recurrent bleeding on therapeutic UFH for 24–48 hours.

Thrombotic Complications of Durable LVAD Support

A comprehensive overview of the pathophysiology of device-related thrombosis is beyond the scope of this chapter and was recently described elsewhere (de Biasi 2015). In brief, because of the inherent lack of hemocompatibility of the blood-contacting surfaces within the pump, thrombus formation begins when activated platelets and the titanium alloy interface by adhesion proteins (e.g., von Willebrand factor). As activated platelets continue to aggregate, local concentrations of tissue factor spike and form complexes with factor VIIa, hence stimulating the extrinsic pathway. Concurrently, contact proteins (e.g., high-molecular-weight kininogen) also adhere to the metal surface of the device and promote further generation of thrombin through the intrinsic pathway. The net result of these converging coagulation cascades is formation of a stabilized clot within the device, which exponentially increases sheer stress on erythrocytes. The ensuing hemolysis perpetuates this vicious cycle by carbon monoxide release, which is itself a procoagulant molecule.

As the clot expands, either within the pump motor itself or in the cannula, device function eventually becomes compromised. Patients usually then begin to manifest clinical signs of device thrombosis, such as overt HF symptoms, cardiogenic shock and organ malperfusion, hemolysis (e.g., elevations in serum lactate dehydrogenase and hematuria), and derangements in device parameters (see Table 2-4). All of the commercially available devices are radio-opaque, and as such, the diagnosis of device thrombosis is based on clinical suspicion and through exclusion of alternative pathologies (Goldstein 2013). Pump-speed change testing, or a ramp test, can be a useful ancillary diagnostic modality in the HeartMate II patient population (Estep 2014). Pharmacotherapy options for the treatment of acute device thrombosis can include UFH, direct thrombin inhibitors (e.g., argatroban), glycoprotein IIb/IIIa inhibitors, and thrombolytic agents. Evidence to support these therapies is limited to case reports and case series; the aggregate experience of these small series suggests that the failure rate for medical therapy is unacceptably high (Jennings 2015).

One notable exception seems to be thrombolysis use with the HeartWare HVAD, but only when this therapy is guided by log file analysis (Jorde 2015). Using log files of power readings stored in the device may identify signals of thrombosis and allow for early intervention before thrombi become too extensive to be treated pharmacologically. Outside this specific scenario, surgical therapy with device exchange should be pursued as first-line treatment of suspected device thrombosis. Pharmacotherapy should be reserved as salvage treatment for those who are not candidates for surgery, keeping in mind that outcomes in this scenario are poor and patients are at risk of hemorrhagic complications.

Clinical pharmacists can also assist with the pharmacologic support of patients during the treatment of device thrombosis. In anticipation of surgery, measures outlined earlier in this chapter (e.g., discontinuation of ACE inhibitor therapy) can be executed. Intravenous UFH can be considered for those with subtherapeutic INR values as a bridge to surgery; however, the benefit of this strategy has not been proven. For patients with cardiogenic shock, inotropic or vasopressor therapy should be implemented for hemodynamic stabilization, and diuretic therapy can be used to decongest those who are hypervolemic.

ORTHOTOPIC HEART TRANSPLANTATION

Orthotopic heart transplantation remains the gold standard surgical treatment for patients with advanced HF. One-year survival after transplantation is greater than 90%, and median survival was recently reported to be greater than 10 years, making this a more definitive solution to treating advanced HF in the appropriately selected population. Because of the limited donor availability relative to prospective recipients, candidates are screened to ensure they are the most qualified (see Table 2-1). As mentioned previously, it is the goal of the care team to optimize a patient's overall condition through positive inotropic medications, nutrition support, and MCS, if needed. Hemodynamically unstable patients or patients with multiorgan dysfunction or severe nutritional deficiencies undergoing transplantation would give rise to dismal outcomes; hence, this is avoided at most centers. According to available statistics published by the International Society for Heart and Lung Transplantation, there is a growing trend of providing MCS to patients with advanced HF before heart transplantation, which was reported in less than 20% of heart recipients in 2000 but increased to about 50% in 2013 (Lund 2015). An evolving relationship and respective place in therapy remains for MCS and OHT in the treatment of advanced HF.

Immunosuppression and Rejection

Immunosuppression is administered to heart transplant recipients beginning intraoperatively to prevent acute cellular and antibody-mediated (humoral) rejection at all phases after transplantation. High doses of intravenous corticosteroids (usually 500–1000 mg of methylprednisolone) are given intraoperatively before the vascular clamps are removed and the new graft is perfused. Many centers (about 50% worldwide) give an additional induction agent in combination with intravenous corticosteroids. According to recent registry data, the most common choice of agent is an interleukin-2 receptor antagonist (basiliximab or daclizumab [no longer available in the United States]), which is given to 30% of OHT recipients. About 20% of OHT recipients receive induction with antithymocyte globulin at the time of transplantation (Lund 2015). Use of induction agents remains controversial

because no clear benefit on long-term survival reported in registry data is associated with their use; however, their use may be considered in patients determined to be at a higher risk of rejection, particularly the use of antithymocyte globulin in patients who have elevated panel reactive antibodies (Lund 2015; Baran 2010).

After surgery, corticosteroids are tapered slowly as calcineurin inhibitors and antiproliferative immunosuppressive agents (mycophenolate mofetil, sirolimus, or azathioprine) are initiated within the first few postoperative days to weeks. Tacrolimus is usually regarded as the preferred calcineurin inhibitor in OHT, and target trough ranges early posttransplantation are 10–15 ng/mL (Lund 2015; Baran 2010). Unlike transplantation of some of organs, use of sirolimus is routinely delayed in heart transplantation given its effect on delayed wound healing. Adjustments to immunosuppression are based on toxicities of agents, graft function, and pathologic evidence of rejection from surveillance biopsy assessment.

Rejection diagnosis and treatment is very complex, and management strategies remain largely controversial. Hence, this chapter will serve as a brief introduction to rejection after OHT. Rejection is generally diagnosed when patients have evidence of graft dysfunction, or it may be diagnosed by routine surveillance biopsies early after OHT. Rejection is classified as cellular mediated or antibody mediated, with cellular rejection occurring more commonly. The diagnosis of rejection largely depends on a histopathologic assessment of an endomyocardial tissue specimen obtained from biopsy, where several techniques and staining are used to identify the presence of lymphocytes, macrophages, and complement deposition and evidence of myocyte damage. The type of rejection present determines the appropriate drug therapies to be considered. If rejection is strongly suggested in a

patient with hemodynamic compromise, high-dose intravenous corticosteroids (500–1000 mg of methylprednisolone) are given before analysis of biopsy specimens (Baran 2010). In severe hemodynamic instability in the presence of rejection, antithymocyte globulin should be considered because it has cytolytic effects for all lymphocytes, including T cells and B cells. According to surveillance biopsy data, the presence of donor-specific antibodies and the patient's known history of antibody-mediated rejection, plasmapheresis, and other drug therapies including rituximab, intravenous immunoglobulin, proteasome inhibitors, eculizumab, or alemtuzumab may be considered to treat antibody-mediated rejection (Table 2-6) (Colvin 2015).

Hemodynamic Support and Arrhythmia Management After OHT

After OHT, patients are expected to receive vasoactive infusions to support cardiac function and systemic vascular resistance as they are transitioned from cardiopulmonary bypass and the transplanted heart begins to assume its role in providing total cardiac output. Patient hemodynamics can be very labile during the early postoperative period and may require frequent assessment and adjustment of vasoactive infusions. In many cases, patients in the immediate postoperative period will have signs of systemic inflammatory response syndrome and may require vasopressors to maintain MAP greater than 60 mm Hg. Cardiac function in heart transplant recipients can be variable in the early postoperative stage, with some patients immediately achieving optimal cardiac output and others taking time to recover. Causes of decreased cardiac output during this time could include rejection or primary graft dysfunction. Rejection at this time is classified as hyperacute because it occurs within minutes to hours of graft reperfusion (Baran 2010). Primary

Table 2-6. Drug Therapies for Antibody-Mediated Rejection

Drug Therapy	Proposed Mechanism of Action	Relative Drug Expense
Corticosteroids	Up-regulation of anti-inflammatory gene expression	\$
Intravenous immunoglobulin	Blocks Fc-γ receptor; inhibits complement; down-regulates B-cell receptor; neutralizes circulating antibody and cytokines	\$\$\$\$
Antithymocyte globulin	Depletes T lymphocytes and some B lymphocytes	\$\$\$
Rituximab	Monoclonal antibody against CD20, depletes B cells	\$\$
Alemtuzumab	Monoclonal antibody against CD52 present on all T and B cells	\$\$
Bortezomib/carfilzomib	26S proteasome inhibitor on plasma cells, depletes B cells and plasma cells	\$\$
Eculizumab	Terminal complement inhibitor	\$\$\$\$\$

Information from: Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management. *Circulation* 2015;131:1608-39.

graft dysfunction is a diagnosis characterized by cardiac dysfunction in the absence of immunologic-mediated injury. Inotropic support should slowly be tapered after OHT, with careful attention to changes in the patient's heart rate.

Inhaled vasodilators including inhaled nitric oxide or prostacyclins may be used to reduce RV afterload or manage RV dysfunction after OHT, which can occur in recipients with elevated pulmonary vascular resistance (PVR) (Costanzo 2010). Typically, these agents are given with inotropes and potentially transitioned to oral phosphodiesterase type 5 inhibitors (e.g., sildenafil), if needed.

Heart transplant recipients may be prone to bradyarrhythmias and sinus node dysfunction because the newly implanted heart was denervated at the time of transplantation. This denervation results in autonomic deregulation of intrinsic heart rate, and instead, natural heart rate is influenced by intrinsic pacemaker potential of cardiac myocytes and circulating catecholamines. Sympathetic denervation results in an impaired ability to generate an increased heart rate response to exercise or other stressors affecting exercise tolerance, and parasympathetic denervation may eventually lead to a higher resting heart rate.

During the early posttransplant period, bradyarrhythmias and relative chronotropic incompetence pose a greater concern to the ICU treatment of OHT patients and usually resolve within days to weeks after transplantation. The target heart rate immediately after transplantation is usually 90–110 beats/minute; however, in select patients, a slower heart rate may be safe as long as rhythm is regular and cardiac output is sufficient (Costanzo 2010). Inotropic agents used provide chronotropic support; however, in select patients, backup pacing may be necessary to maintain a heart rate sufficient to support cardiac output. Isoproterenol is generally regarded as the intravenous drug of choice to manage chronotropic incompetence; however, recent increases in isoproterenol acquisition costs have led clinicians to consider alternatives, including dobutamine, dopamine, and epinephrine, depending on the other patient-specific factors (e.g., blood pressure, cardiac output).

All chronotropic agents have the potential to elicit tachyarrhythmias, including ventricular tachycardia, making ongoing telemetry monitoring critical to ensure the safety of these agents. Oral drug therapies including terbutaline and theophylline have been used with anecdotal success in transitioning patients from intravenous chronotropic support (Costanzo 2010; Coons 2004; Bertolet 1996; Redmond 1993; Ellenbogen 1988). Tachyarrhythmias may often be managed simply by reducing the use of chronotropic infusions, when present; however, occasionally, nonpharmacologic cardioversion of malignant arrhythmias may be necessary. Amiodarone has been used in patients after heart transplantation to treat both atrial and ventricular arrhythmias; however, its use should always be considered temporary because the long-term toxic effects on the transplanted heart and other organs are

undesirable (Costanzo 2010). Digoxin is generally considered ineffective as a rate-controlling agent after heart transplantation, and agents with negative inotropic properties should be avoided in the early postoperative period after OHT (Costanzo 2010; Stecker 2005). Attention should be paid to relevant drug-drug interactions if amiodarone is used in the presence of calcineurin inhibitors because amiodarone is known to increase drug exposure (Page 2005).

Antimicrobial Prophylaxis and Infectious Complications

Given the immunosuppression required to prevent rejection in patients after OHT, the clinical pharmacist should be particularly aware of any infectious complications, especially in the postoperative ICU phase. Patients are routinely given standard antibacterial prophylaxis around the time of surgery, which should include coverage of skin flora (e.g., MRSA). Because many patients with ventricular assist devices may undergo transplant with chronic device infections, an appropriate treatment course tailored to microbiologic culture data after transplantation after device removal should be considered (Costanzo 2010).

Opportunistic infections are uncommon within the first month after transplantation; however, guidelines indicate

Practice Points

In determining the optimal treatment plan for ECMO patients, the clinical pharmacist should monitor and optimize the following aspects of therapy:

- The cause of hemodynamic decompensation leading to the need for ECMO should be determined to ensure effective treatment of the underlying causes (e.g., arrhythmia, pulmonary embolism, progressive systolic HF, acute coronary syndrome).
- Anticoagulation should be evaluated according to laboratory and clinical values and adjusted to minimize risk of thromboembolic complications while the patient is receiving ECMO support. Bleeding should be monitored carefully because these patients remain at high risk of coagulopathy and major bleeding throughout support.
- Vasoactive therapies may be adjusted to target mean arterial blood pressure of 60–90 mm Hg. Inotropes may be used to enhance pulsatility in patients receiving VA ECMO to minimize the risk of intracardiac thrombus formation and facilitate weaning from MCS.
- Patients receiving ECMO should be monitored carefully for infection because of several risk factors. Prophylactic antimicrobial strategies may be considered, and in patients with signs/symptoms of infection, broad-spectrum antibacterial and antifungal therapy should be initiated and adjusted according to the available cultures.
- Analgesia and sedation therapies should be tailored to patient-specific needs with the goals of achieving ventilation/perfusion goals, ensuring the patient's safety, and minimizing long-acting sedating agents or agents that could negatively affect the patient's hemodynamics.

the initiation of *Pneumocystis jiroveci* pneumonia (PJP), cytomegalovirus (CMV), and mucocutaneous *Candida* prophylaxis within the first few days postoperatively (Costanzo 2010; Fishman 2007). Sulfamethoxazole/trimethoprim is considered the gold standard for PJP prophylaxis in patients after OHT. Alternatives can be considered for patients with sulfa allergies, hyperkalemia, or other potential adverse effects related to sulfamethoxazole/trimethoprim.

Antiviral prophylaxis should be based on donor and recipient CMV immunoglobulin G (IgG) matching to determine the risk level and need for dual CMV plus herpes simplex virus (HSV) prophylaxis versus HSV-only prophylaxis. Donor-positive CMV IgG and recipient-negative CMV IgG is considered high risk, any recipient-positive CMV IgG is considered intermediate risk, and both donor- and recipient-negative CMV IgG is considered low risk. Prophylaxis with valganciclovir is generally recommended for both intermediate- and high-risk patients, whereas acyclovir or valacyclovir prophylaxis is appropriate for low-risk patients (Costanzo 2010). Some centers follow preemptive therapy with weekly monitoring of CMV antigen titers instead of routine prophylaxis in intermediate-risk patients, in which case patients should be receiving acyclovir-based prophylaxis to prevent other types of herpes viral infections.

Systemic antifungal prophylaxis is not currently a standard practice for all patients undergoing OHT; however, an analysis showed that those who, before transplantation, are receiving ECMO, receiving renal replacement therapy, or have *Aspergillus* airway colonization may be at a greater risk of invasive fungal infections after OHT (Tissot 2014). Current standard prophylaxis for oropharyngeal candidiasis is nystatin 400,000–600,000 units four times daily or oral clotrimazole lozenges beginning after the patient is extubated postoperatively (Costanzo 2010).

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Self-Assessment Questions

21. A 32-year-old man with idiopathic dilated cardiomyopathy is admitted to the ICU for worsening cardiorenal syndrome on the telemetry ward. He is currently listed for orthotopic heart transplantation (OHT). A pulmonary artery catheter is placed; it reveals an elevated pulmonary capillary wedge pressure (PCWP), a low cardiac index, and a rising serum lactate concentration. The patient's heart rate is 102 beats/minute and blood pressure is 80/57 mm Hg. In addition to intravenous furosemide, which drug therapy regimen would be best to initiate for this patient?
- A. Milrinone
 - B. Dobutamine
 - C. Epinephrine
 - D. Dobutamine and norepinephrine
22. A 46-year-old man presents with acute myocardial infarction and cardiogenic shock. He undergoes percutaneous coronary intervention with drug-eluting stent placement to the left-anterior descending and right coronary arteries. An Impella 2.5 device is used for hemodynamic support. Unfortunately, the patient remains dependent on percutaneous left ventricular assist device (pVAD) and inotrope support. He is subsequently listed for heart transplantation as status 1a, and he will remain in the ICU until he receives an organ. He has a relatively uncommon blood type, so he is expected to receive a transplant within 1–2 weeks at status 1a. His drug regimen includes ticagrelor and aspirin. Which one of the following, in addition to discontinuing ticagrelor, is best to recommend for this patient?
- A. Initiate eptifibatid therapy.
 - B. Initiate clopidogrel therapy.
 - C. Continue aspirin monotherapy.
 - D. Initiate cangrelor therapy.

Questions 23 and 24 pertain to the following case.

J.T. is a 56-year-old man (weight 65 kg) who is admitted with acute anterior ST-segment elevation myocardial infarction (STEMI) with severe refractory cardiogenic shock requiring Impella CP support. He arrives in the ICU with a purge solution containing 25,000 units of heparin in a 500-mL solution of 5% dextrose. The purge is flowing at 16 mL/hour. J.T.'s current activated PTT (aPTT) value is 78 seconds (goal 60–80 seconds). J.T.'s complete blood count lab values are all within normal limits.

23. Which one of the following is best to recommend regarding anticoagulation therapy for J.T.?
- A. Discontinue heparin from the purge solution and place him on intravenous heparin 800 units/hour.
 - B. Add intravenous heparin at 300 units/hour to the current regimen.
 - C. Continue the current regimen and recheck an aPTT value in 6 hours.
 - D. Discontinue heparin from the purge solution and initiate argatroban therapy.
24. Two hours after J.T.'s arrival to the ICU, the nurse inspects the controller for the Impella CP, and the purge rate has decreased to 10 mL/hour. Which one of the following changes to the anticoagulation regimen would be best for J.T.?
- A. Discontinue heparin from the purge solution and place him on intravenous heparin 800 units/hour.
 - B. Add intravenous heparin at 300 units/hour to the current regimen.
 - C. Continue the current regimen and recheck an aPTT value in 4 hours.
 - D. Discontinue heparin from the purge solution and initiate argatroban therapy.
25. A 65-year-old woman with a history of stage D ischemic cardiomyopathy is postoperative day 2 from a HeartMate II implantation. The patient's MAP is 97 mmHg, and she is receiving dobutamine for right ventricular (RV) support. She is receiving no other vasoactive or antihypertensive medications. Her latest Svo₂ is 55%, and her ScR is 1.6 mg/dL (baseline before surgery was 1.0 mg/dL). Which one of the following is best to recommend for this patient?
- A. Wean off dobutamine.
 - B. Initiate enalaprilat 0.625 mg intravenously every 6 hours.
 - C. Initiate hydralazine 10 mg intravenously every 6 hours.
 - D. Initiate nicardipine 5 mg/hour intravenous drip.
26. Which one of the following patients receiving a continuous-flow left ventricular assist device with suspected RV failure would most benefit from therapy with inhaled iloprost?
- A. PCWP elevated, pulmonary vascular resistance (PVR) elevated, device flow low
 - B. PCWP low, PVR elevated, device flow low
 - C. PCWP low, PVR normal, device flow low
 - D. PCWP elevated, PVR normal, device flow low
27. A 76-year-old man with a history of ischemic cardiomyopathy and ventricular arrhythmia undergoes implantation with a HeartMate II device. On postoperative day 2, the patient has dizziness and palpitations and sustained ventricular tachycardia. His hemodynamic parameters are stable, and esmolol 25 mcg/kg/minute is initiated.

Subsequently, the patient's central venous pressure increases, whereas his blood pressure, device flow, and pulsatility index all decrease. Which one of the following changes would be most appropriate for this patient?

- A. Continue esmolol; start milrinone.
 - B. Discontinue esmolol; start amiodarone.
 - C. Discontinue esmolol; start lidocaine.
 - D. Continue esmolol; start amiodarone.
28. A 68-year-old woman with a HeartWare HVAD presents with sudden-onset right-sided weakness and aphasia; she is given a diagnosis of an intraparenchymal hemorrhage of the left parietal and temporal lobe, with intraventricular extension into the third and fourth ventricles. The patient becomes unresponsive and is admitted to the neurology ICU after being intubated for airway protection. Her INR is 2.9, and the team is considering anticoagulation reversal. Which one of the following is best to recommend for this patient?
- A. 4-factor prothrombin complex concentrate (PCC) with intravenous vitamin K
 - B. 3-factor PCC with intravenous vitamin K
 - C. Fresh frozen plasma with intravenous vitamin K
 - D. Intravenous vitamin K alone
29. A 32-year-old man with a history of nonischemic dilated cardiomyopathy after a HeartMate II implant 8 months ago presents with fever, leukocytosis, and hypotension. Visual inspection of the percutaneous driveline suggests infection. The patient is found to have an acute kidney injury and an elevated lactate, and vasopressor therapy is initiated for hemodynamic support. He is transferred to the medical ICU with a diagnosis of septic shock. Which one of the following antimicrobial regimens would be best to recommend for this patient?
- A. Cefazolin plus levofloxacin plus fluconazole
 - B. Vancomycin plus ceftriaxone plus micafungin
 - C. Vancomycin plus cefepime plus fluconazole
 - D. Cefepime plus levofloxacin plus micafungin
30. A 65-year-old man with a history of ischemic dilated cardiomyopathy is now postoperative day 2 from a HeartWare HVAD implant. Surgical hemostasis has been achieved, and the team would like to begin a thromboprophylactic regimen. The patient was taking warfarin 5 mg daily for atrial fibrillation before his surgery. No genotype data are available regarding his warfarin sensitivity. The patient has not been initiated on any new medications that interact with warfarin. Which one of the following is best to recommend for this patient?
- A. Heparin 45–50 seconds, aspirin 325 mg daily, warfarin 5 mg daily
 - B. Heparin 60–80 seconds, aspirin 325 mg daily, warfarin 5 mg daily

- C. Heparin 45–50 seconds, aspirin 81 mg daily, warfarin 5 mg daily
- D. Heparin 45–50 seconds, aspirin 325 mg daily, warfarin 2.5 mg daily

31. A 24-year-old woman with a history of peripartum cardiomyopathy after a HeartMate II implant 4 months ago is readmitted to the hospital with pulmonary edema and severe fatigue. Her laboratory studies are notable for an elevated SCr (1.6 mg/dL, previously 0.8 mg/dL), INR 2.8, and serum lactate dehydrogenase 4285 IU/L (normal less than 250 IU/L). Her blood pressure is stable; however, her flow and power readings on the device are elevated. She is transferred to the cardiac ICU for close monitoring. Further testing shows Svo₂ 56% and lactate 2.8 mg/dL. A pump speed change test suggests device thrombosis. Which one of the following treatment plans is best to recommend for this patient?
- A. Surgical device exchange
 - B. Intravenous alteplase
 - C. Intravenous heparin
 - D. Intravenous milrinone

Questions 32–35 pertain to the following case.

A.J. is a 65-year-old man (weight 73 kg) with a medical history of diabetes, hypertension, and dyslipidemia. He presents with a STEMI and is emergently taken to the cardiac catheterization laboratory, where he undergoes percutaneous coronary intervention with a drug-eluting stent in the proximal left anterior descending coronary artery. Immediately afterward, he has a ventricular fibrillation arrest. Resuscitation measures are initiated immediately according to the advanced cardiovascular life support guidelines, and A.J. is defibrillated several times. However, his unstable cardiac rhythm persists, and he is placed on VA ECMO by peripheral cannulation in the catheterization laboratory. A.J. is brought to your ICU for further treatment. His vital signs are heart rate 120 beats/minute, rhythm sinus tachycardia, blood pressure 125/90 mm Hg, MAP 102 mm Hg, Sao₂ 97% on mechanically ventilated fraction of inspired oxygen (Fio₂) 60%, and ECMO Fio₂ 100%. The ECMO flow is 2.8 L/minute at 3500 rpm. In the catheterization laboratory, A.J. receives heparin 10,000 units intravenously x 1 dose, vancomycin 1 g intravenous piggyback x 1 dose, ticagrelor 180 mg by orogastric tube (OGT) x 1 dose, amiodarone 300 mg intravenously x 1 dose followed by continuous infusion 1 mg/minute, epinephrine 1 mg intravenously x 3 doses, and lidocaine 100 mg intravenously x 1 dose. In the ICU, A.J. receives aspirin 81 mg by OGT daily, ticagrelor 90 mg by OGT twice daily, pantoprazole 40 mg intravenous push daily, amiodarone 1 mg/minute, and epinephrine 12 mcg/minute.

32. Which one of the following is best to recommend regarding anticoagulant therapy for A.J.?

- A. Immediately initiate fixed-dose heparin at 400 units/hour, and send activated clotting time (ACT), aPTT, and anti-Xa 6 hours later.
 - B. Send CBC, aPTT, anti-Xa, and ACT immediately as stat to assess the stability of hemoglobin and degree of anticoagulation remaining from 10,000 units given in the catheterization laboratory.
 - C. Initiate venous thromboembolism prophylaxis with heparin 5000 units subcutaneously every 8 hours; the patient has no indication for therapeutic anticoagulation.
 - D. Initiate enoxaparin 70 mg every 12 hours for therapeutic anticoagulation.
33. Which one of the following is best to recommend regarding A.J.'s vasoactive continuous infusions?
- A. Make no changes; the patient is stable.
 - B. Add nitroglycerin to lower preload and facilitate weaning of ECMO.
 - C. Taper the epinephrine dose in an attempt to lower MAP to less than 90 mm Hg.
 - D. Add esmolol because the target heart rate in patients with acute coronary syndrome is 50–60 beats/minute.
34. Which one of the following is best to recommend as initial antimicrobial prophylaxis for A.J.?
- A. Give vancomycin and cefepime dosed according to renal function and dialysis.
 - B. Give vancomycin only, dosed according to renal function and dialysis.
 - C. No further antimicrobial prophylaxis is indicated; if evidence of infection, initiate broad-spectrum antibiotics.
 - D. Give cefazolin only, dosed according to renal function and dialysis.
35. Two days into ECMO support, A.J.'s intravenous heparin requirements continue to increase, and he now receives a dose of 45 units/kg/hour (yesterday's dose was 35 units/kg/hour). His Hgb remains stable, and his coagulation studies show aPTT 48 seconds, anti-Xa 0.15, and ACT 155 seconds. Which one of the following best explains A.J.'s escalating dose requirements of heparin?
- A. The patient has excessive endogenous production of thrombin; change heparin to argatroban.
 - B. The patient has acquired antithrombin III (AT III) deficiency; assess AT activity level and consider replacement with recombinant AT III.
 - C. There are no major problems with the patient's anticoagulation; continue to titrate heparin to target aPTT 1.5–2.5 times normal.
 - D. The patient's anticoagulation currently appears to be within the therapeutic range; continue current regimen.

Questions 36 and 37 pertain to the following case.

K.K. is a 58-year-old man (weight 78 kg) who has been receiving ECMO support for 2 days while neurologically recovering from cardiac arrest. He appears very agitated and diaphoretic, and he is breathing dyssynchronously with the ventilator. K.K. is responding appropriately to basic commands, but he is persistently trying to reach for his femoral arterial cannulation site, despite being physically restrained. The following pain/sedation/agitation scale values were documented in the patient's updated flowsheet: CPOT (Critical Care Pain Observation Tool) +5, RASS (Richmond Agitation-Sedation Scale) +2, CAM-ICU (confusion assessment method for the ICU) negative. K.K.'s current sedation/analgesia regimen includes intravenous fentanyl 200 mcg/hour and midazolam 4 mg/hour.

36. His care team asks for your assessment of K.K.'s current sedation/analgesia regimen. According to your assessment, which one of the following best describes K.K.'s clinical status?
- A. Both fentanyl and midazolam may have significant drug loss or sequestration within the ECMO circuit, and he may be experiencing poor pain control.
 - B. He is likely an illicit drug user, explaining his abnormal tolerance to sedation/analgesic agents.
 - C. He has alcohol withdrawal syndrome and will likely need a multivitamin/folic acid/thiamine and seizure prophylaxis with chlordiazepoxide.
 - D. He has severe ICU delirium, likely worsened by fentanyl and midazolam.
37. Which one of the following is best to recommend for K.K.?
- A. Give haloperidol 2 mg intravenous push every 10 minutes x 3 doses or until agitation subsides; continue current fentanyl and midazolam infusions.
 - B. Change fentanyl to hydromorphone and midazolam to lorazepam, and continue to titrate according to patient response.
 - C. Increase fentanyl to 300 mcg/hour, and initiate quetiapine 25 mg every 8 hours by OGT to treat ICU delirium.
 - D. Make no changes because this behavior is expected in any patient receiving ECMO support.

Questions 38–40 pertain to the following case.

T.H. is a 65-year-old African American man with a history of stage D ischemic cardiomyopathy. He underwent OHT after waiting as status 1A on milrinone with an intra-aortic balloon pump for 4 weeks and is now postoperative day 0 in your cardiothoracic ICU. T.H. received 1000 mg of methylprednisolone and 20 mg of basiliximab in the operating room for induction immunosuppression. His urinary output since returning from the operating room is 0.3 mL/kg/hour. The organ donor was cytomegalovirus (CMV) IgG positive, and T.H. is CMV IgG

negative. His current vital signs are heart rate 72 beats/minute, normal sinus rhythm, blood pressure 90/55 mm Hg (MAP 67 mm Hg), cardiac index 1.9 L/minute/m², cardiac output 3.1 L/minute, Svo₂ 48%, lactic acid 7.5 mmol/L, central venous pressure 15 mm Hg, PA 41/15 mm Hg, and PCWP 20 mm Hg. His arterial blood gas is Po₂ 120 mm Hg, Pco₂ 42 mm Hg, HCO₃ 15 mEq/L, Sao₂ 99%, and Hct 30%. T.H.'s scheduled drugs include basiliximab 20 mg intravenously x 1 dose postoperative day 4, methylprednisolone 125 mg every 8 hours with subsequent tapering, nystatin 500,000 units (5 mL) swish and swallow four times daily after extubation, pantoprazole 40 mg intravenously daily, cefepime 1 g intravenously every 8 hours, vancomycin 1.25 g intravenously every 12 hours, norepinephrine 6 mcg/minute, and vasopressin 0.04 unit/minute.

38. T.H. has just returned to the ICU, and laboratory tests are currently pending. Which one of the following is best to recommend for T.H.?
- A. Add dobutamine intravenously to target a heart rate of 90–100 beats/minute while decreasing norepinephrine and vasopressin, if possible, to maintain a MAP greater than 60 mm Hg.
 - B. The patient still requires additional transfusion of packed red blood cells because he has hypoperfusion characterized by hemorrhagic shock from surgery.
 - C. Add nitric oxide at 20 ppm inhaled to decrease PVR.
 - D. Give bumetanide 1 mg intravenous push, and start a continuous infusion at 1 mg/hour.
39. On postoperative day 2, T.H. has been extubated and is progressing well by all indications, according to the medical team. His heart rate is 95 beats/minute, and cardiac index has improved to 2.9 L/minute/m². Transthoracic echocardiogram reveals a left ventricular ejection fraction (LVEF) of 55%–60%. Given the available information, which one of the following is best to recommend for T.H.?
- A. Give antithymocyte globulin 1.5 mg/kg intravenously because the patient's presentation is consistent with hyperacute rejection.
 - B. Initiate sirolimus 1 mg orally daily.
 - C. Initiate tacrolimus 1 mg orally twice daily.
 - D. Discontinue basiliximab because the patient is clinically progressing well.
40. Which one of the following is best to recommend regarding CMV prophylaxis for T.H.?
- A. Start valganciclovir 900 mg orally daily within 48 hours of transplantation.
 - B. Start valacyclovir 500 mg orally twice daily 72 hours after transplantation.
 - C. Monitor for CMV viremia with weekly CMV PCR.
 - D. Do not initiate antiviral prophylaxis.

Learner Chapter Evaluation: Advanced Heart Failure.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. The content of the chapter met my educational needs.
21. The content of the chapter satisfied my expectations.
22. The author presented the chapter content effectively.
23. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
24. The content of the chapter was objective and balanced.
25. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
26. The content of the chapter was useful to me.
27. The teaching and learning methods used in the chapter were effective.
28. The active learning methods used in the chapter were effective.
29. The learning assessment activities used in the chapter were effective.
30. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

31. Design optimal pharmacotherapy for patients awaiting left ventricular assist device (LVAD) implantation or orthotopic heart transplantation (OHT).
32. Construct safe and effective drug therapy regimens for patients receiving extracorporeal membrane oxygenation support.
33. Devise effective thromboprophylactic strategies for patients receiving percutaneous LVAD support.
34. Design effective treatment plans for patients with complications of durable LVAD therapy.
35. Devise safe and effective pharmacotherapy regimens in patients recovering from OHT.
36. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
37. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:



Management of Circulatory Shock

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LEARNING OBJECTIVES

1. Distinguish between the various shock syndromes according to a patient's clinical and hemodynamic parameters.
2. Construct an initial resuscitation pathway that includes quantitative resuscitation for patients with shock.
3. Devise a treatment strategy for a patient with hypovolemic shock.
4. Design an appropriate resuscitation and treatment strategy for a patient with cardiogenic shock.
5. Delineate the role and place in therapy of thrombolytics for pulmonary embolism.
6. Develop a treatment pathway for the care of patients with severe sepsis or septic shock that incorporates the Surviving Sepsis Campaign guideline recommendations and management bundle.

ABBREVIATIONS IN THIS CHAPTER

CO	Cardiac output
CVP	Central venous pressure
Do ₂	Oxygen delivery
IVC	Inferior vena cava
LV	Left ventricular
MAP	Mean arterial pressure
MI	Myocardial infarction
PAC	Pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
PE	Pulmonary embolism
PH	Pulmonary hypertension
PLR	Passive leg raising
PPV	Pulse pressure variation
PRBC	Packed red blood cell
PVR	Pulmonary vascular resistance
RV	Right ventricular
SBP	Systolic blood pressure
SV	Stroke volume
SVR	Systemic vascular resistance
SVV	Stroke volume variation
Vo ₂	Oxygen consumption

[Table of common laboratory reference values.](#)

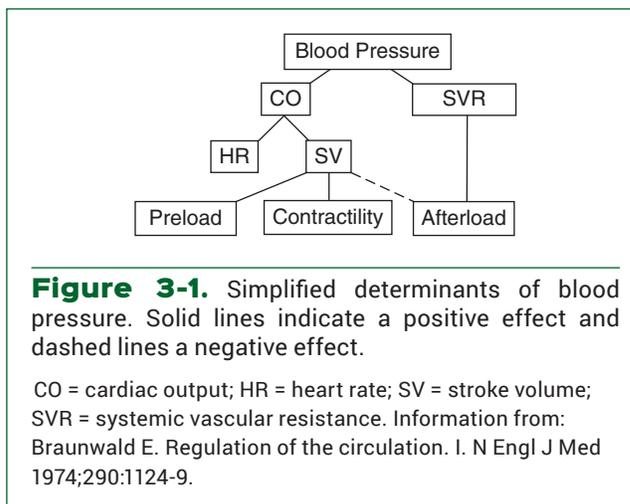
INTRODUCTION

Circulatory shock is a heterogeneous group of syndromes best described as acute circulatory failure that are typically classified into one of four etiologic mechanisms: (1) hypovolemic, (2) cardiogenic, (3) obstructive, or (4) vasodilatory/distributive. However, the different shock syndrome types often coexist. These syndromes, which arise when tissue perfusion or oxygen delivery (Do₂) is inadequate to perform vital metabolic functions, are commonly encountered in the ICU, with about one in three patients receiving vasoactive medications to treat circulatory shock during their ICU stay (Sakr 2006). Thus, clinical pharmacists must have a thorough understanding of cardiovascular physiology, hemodynamic monitoring methods and parameters, and treatment of circulatory shock.

The clinical presentation of a patient with shock may be extreme or subtle. In most cases, shock is first identified by the presence of arterial hypotension with associated tachycardia. Although threshold values of systolic blood pressure (SBP) less than 90 mm Hg or mean arterial pressure (MAP) less than 70 mm Hg are commonly used, higher SBP or MAP values may be necessary to prevent tissue hypoperfusion in some patients (e.g., those with chronic hypertension). Patients with normal-appearing blood pressure (either by compensation or by an adjusted zone of auto-regulation) may have other clinical signs consistent with inadequate tissue perfusion. Clinical manifestations of tissue hypoperfusion that occur at the bedside include cutaneous (e.g., cool, clammy, or mottled skin;

decreased capillary refill), renal (urinary output less than 0.5 mL/kg/hour), and neurologic (e.g., confusion, obtundation). These signs of hypoperfusion must be interpreted in the context of patient history (e.g., end-stage renal disease with anuria) and concomitant therapies (e.g., sedative administration). In addition, patients with shock usually have hyperlactatemia (above 2 mmol/L) suggestive of abnormal cellular oxygen use.

The fundamental role of the cardiovascular system is to supply the tissues with oxygen. Mean arterial pressure is the driving pressure for peripheral blood flow and end-organ perfusion; sufficient arterial pressure allows redistribution of cardiac output (CO) to vital organs. Therefore, both adequate MAP and adequate Do_2 are necessary to meet



BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Cardiovascular physiology
- Calculation of oxygen delivery and the influence of the individual components on oxygen delivery
- General knowledge of the pathophysiology that leads to circulatory shock
- Composition of resuscitation fluids and risks of administration
- Vasoactive medication pharmacology and pharmacodynamics effects
- Risk factors for bleeding after administration of thrombolytics for pulmonary embolism

[Table of common laboratory reference values.](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Huang YC. [Monitoring oxygen delivery in the critically ill.](#) Chest 2005;128:554S-60S.
- Vincent JL, De Backer D. [Circulatory shock.](#) N Engl J Med 2013;369:1726-34. Available at www.nejm.org/doi/full/10.1056/NEJMra1208943#t=article
- Vincent JL, Ince C, Bakker J. [Clinical review: circulatory shock—an update: a tribute to Professor Max Harry Weil.](#) Crit Care 2012;16:239.
- Hollenberg SM. [Vasoactive drugs in circulatory shock](#) Am J Respir Crit Care Med 2011;183:847-55.
- Surviving Sepsis Campaign. [Guidelines, Bundles, and Implementation Tools](#) [homepage on the Internet].

tissue metabolic requirements. Inadequate Do_2 for the level of oxygen consumption (Vo_2) may result in organ dysfunction, which occurs in under-resuscitated circulatory shock. Determinants of blood pressure are complex, but they can be simplified for bedside use (Figure 3-1).

The amount of oxygen transported to the tissues is described by the Fick CO equation, which states: Do_2 (mL/minute) = $10 \times CO$ (L/minute) $\times Cao_2$, where Cao_2 is the arterial oxygen content. Cao_2 can further be defined as $Cao_2 = (1.34 \times \text{hemoglobin} \times Sao_2) + (0.003 \times Pao_2)$. Increases in hemoglobin and CO most efficiently result in increased Do_2 , but hemoglobin targets (typically above 7 g/dL) are often set independently from Do_2 . Consequently, the typical therapeutic target for a low Do_2 is augmenting CO.

MONITORING TECHNIQUES

Hemodynamic Parameters and Hemodynamic Monitoring Devices

Monitoring hemodynamic parameters is a functional tool that may be used to estimate physiological performance and reserve and, in turn, direct therapy. Hemodynamic parameters can either be directly measured from a monitoring device or calculated according to direct measurements (see [Online Appendix](#)). A single hemodynamic parameter does not show the complete hemodynamic picture; instead, hemodynamics must be interpreted in the context of other parameters. In addition, by itself, a monitoring device cannot improve patient-centered outcomes. Therefore, hemodynamic monitoring devices (see [Online Appendix](#)) are simply tools to gain more information about a patient's hemodynamic profile and must be paired with evidence-based therapies to improve patient outcomes.

Markers of Tissue Perfusion

Monitoring for signs consistent with tissue hypoperfusion is vital to the care of patients with circulatory shock. If tissue hypoperfusion is present, therapeutic interventions should quickly be undertaken to restore adequate tissue perfusion. Tissue perfusion can be conceptualized as either global or regional, with markers relative to each.

Global Tissue Perfusion

As noted previously, bedside observations can assess for end-organ function and may be consistent with global tissue hypoperfusion. Patients with altered mental status, low urinary output, or mottled skin likely have inadequate perfusion. In addition, skin temperature may be used as an approximation (surrogate) of systemic vascular resistance (SVR), in which warm skin temperature suggests decreased SVR (vasodilation) and cold skin temperature suggests increased SVR (vasoconstriction).

An elevated blood lactate concentration also suggests global tissue hypoperfusion. Lactic acidosis is typically divided into types A and B. Type A lactic acidosis occurs in Do_2/Vo_2 mismatch (oxygen demand exceeds supply). Type B lactic acidosis is not related to tissue hypoxia and typically occurs in impaired lactate clearance or medication-related causes (e.g., metformin, epinephrine, or linezolid). Elevated lactate concentrations may be the result of increased production, decreased clearance, or both. The presence of severe liver dysfunction may impair lactate clearance and accentuate lactate concentration elevations in shock. Elevated lactate concentrations may also indicate regional tissue hypoperfusion (e.g., mesenteric ischemia or critical limb ischemia). Therefore, the source of lactate concentration elevation must be evaluated.

Venous oximetry is also a useful monitoring tool to assess for global tissue perfusion. The $Scvo_2$ and Svo_2 values are the oxyhemoglobin saturation of venous blood obtained from a thoracic central vein and the pulmonary artery, respectively, and are expressed as a percentage. Of importance, the oxyhemoglobin saturation of blood obtained from a femoral central venous catheter should not be used as a marker of perfusion and cannot be used interchangeably with an $Scvo_2$ obtained from a thoracic central venous catheter. The Svo_2 is a more accurate representation of systemic oxygen extraction because it represents the mixing of venous blood from the superior vena cava, inferior vena cava (IVC), and coronary sinus.

In a healthy patient, Do_2 far exceeds Vo_2 , and cells function with normal aerobic metabolism. When Do_2 is inadequate for Vo_2 , the oxygen extraction ratio is increased to meet tissue oxygen demands, and Svo_2 decreases. Therefore, a decreased $Scvo_2$ or Svo_2 shows that tissue oxygen demands are not completely met by Do_2 . When hemoglobin and arterial oxygen saturation are assumed to be stable, $Scvo_2$ or Svo_2

may be used as a surrogate for CO. In general, Svo_2 above 70% is considered adequate, whereas Svo_2 less than 40% is considered critically low and approaches the critical oxygen extraction ratio (anaerobic metabolism will occur, and lactate concentrations will increase). By themselves, Svo_2 values of 50%–70% do not lead to firm conclusions about the oxygen extraction ratio; these must be interpreted in the context of other markers of tissue perfusion. However, Svo_2 values above 80% likely indicate poor tissue oxygen extraction capacity. This may occur because of the heterogeneity of micro- and macrovascular blood flow (i.e., microcirculatory dysfunction), peripheral shunting of oxygen past the tissues, or impaired mitochondrial oxygen use (Walley 2011).

Regional Tissue Perfusion

Traditional resuscitative strategies have focused on hemodynamic and Do_2 end points (the “macrocirculation”), but the microcirculation plays a key role in tissue oxygenation in shock (particularly in septic shock) and has historically been overlooked. The microcirculation consists of arterioles, capillaries, and venules and is where oxygen release to the tissues occurs. Of importance, microcirculatory blood flow (and Do_2) cannot be predicted by global (macrocirculatory) hemodynamics (De Backer 2007). Studies have shown that the microcirculation is often altered in patients with sepsis; persistent microvascular alterations are associated with multisystem organ failure and death, alterations are more severe in non-survivors than in survivors, and improvements in microcirculatory blood flow correspond with improved patient outcomes (De Backer 2013; Sakr 2004; De Backer 2002). Evaluation of the microcirculation is not commonly used in clinical practice because it requires extensive user experience to obtain proper measurements and time to analyze the results. However, this is an attractive marker of tissue perfusion that, with technical advances, may be used more commonly in the future.

DIFFERENTIATION OF SHOCK STATES

Differentiation of shock states is based on an assessment of a patient’s hemodynamic profile, consisting of preload (central venous pressure [CVP] or pulmonary capillary wedge pressure [PCWP]), CO ($Scvo_2$ or Svo_2 may serve as a surrogate), and afterload (SVR) (Table 3-1). Values to describe this hemodynamic profile have historically been obtained from a pulmonary artery catheter (PAC), but bedside echocardiography is now recommended as the preferred modality to initially evaluate the type of shock (Cecconi 2014). Echocardiography surrogates for preload and CO are defined as left ventricular (LV) size and ventricular function or LV outflow tract velocity time integral, respectively. Of note, the hemodynamic profiles in Table 3-1 occur exclusively in the stated shock state, but in practice, patients often have features of combined or mixed shock states.

Table 3-1. Hemodynamic Profiles of Shock States

Shock State	CVP	PCWP	CO	SVR
Hypovolemic	↓ ^a	↓ ^a	↓	↑
Cardiogenic	↑	↑	↓ ^a	↑
Obstructive				
Impaired diastolic filling (e.g., cardiac tamponade)	↑	↑	↓ ^a	↑
Impaired systolic contraction (e.g., massive PE)	↑	↓ or ↔	↓ ^a	↑
Vasodilatory/distributive				
Pre-resuscitation	↓	↓	↓	↓ ^a
Post-resuscitation	↑	↑	↑	↓ ^a

^aPathophysiologic hallmark of shock state.

PE = pulmonary embolism.

Information from: Vincent JL, De Backer D. Circulatory shock. *N Engl J Med* 2013;369:1726-34; and Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:946-55.

RESUSCITATION PARAMETERS AND END POINTS

The approach to treating a patient with circulatory shock can be divided into four phases, each having different (and sometimes overlapping) treatment goals and therapeutic strategies (Vincent 2013). The initial phase is focused on salvage, in which a minimum acceptable perfusion pressure and CO must be achieved to maintain the patient's survival. Treatment of the underlying causes of the patient's shock, which are lifesaving measures, should be undertaken at this time. Examples of these measures include antimicrobials for sepsis, revascularization for acute myocardial infarction (MI), and surgical hemostasis for trauma. Optimization is the second phase, where the goal is to ensure adequate Do_2 . In the third phase, patient stabilization is targeted, with the goal of preventing (further) end-organ dysfunction. The fourth phase is de-escalation, in which goals of therapy include vasoactive medications weaning (or cessation) and fluid elimination. Although the remainder of this chapter will focus on the first two phases, understanding the phase of a patient's circulatory shock is essential for establishing treatment goals and subsequent therapeutic approaches.

In each shock resuscitation phase, a minimum blood pressure target must be achieved because blood pressure is the driving force for peripheral blood flow and dispersion of the CO, which is vital to ensuring sufficient end-organ perfusion. The MAP is the true driving pressure for peripheral blood flow and is preferred to SBP as a therapeutic target in most shock states. The therapeutic target for a patient in shock is usually a MAP greater than 65 mm Hg or an SBP greater than 90 mm Hg, but this must be individualized according to perfusion assessments. Of importance, MAP is an

insensitive hemodynamic resuscitation parameter because it is influenced by many hemodynamic variables (e.g., blood pressure may be at goal while CO is inadequate). Therefore, additional resuscitation parameters should be used to ensure that all hemodynamic components that may influence end-organ perfusion and Do_2 are optimized. These additional resuscitation goals typically include ensuring (1) adequate end-organ perfusion, (2) lack of fluid responsiveness, and (3) adequate Do_2 .

Adequate End-Organ Perfusion

As MAP decreases, the perfusion pressure of the organ decreases, and subsequently, organ function decreases. Each organ has a critical perfusion pressure that must be exceeded to maintain adequate perfusion, which is organ- and patient-specific (because of adaptation for chronic conditions). Consequently, organ perfusion is best assessed clinically on a per-patient basis. General goals of therapy include resolution of altered mental status and adequate urinary output (above 0.5 mL/kg/hour). These goals may be challenging to assess in patients who are given medications that mask the ability to assess the organ function or in those with chronic organ dysfunction.

Lack of Fluid Responsiveness

Intravenous fluids are given to increase preload and subsequently increase stroke volume (SV), CO, and Do_2 in most shock states. Despite their ubiquitous use, fluids should be given only if there is ineffective organ perfusion and the patient is fluid responsive. Fluid responsiveness is defined as at least a 10%–15% increase in CO after fluid administration. In one systematic review, only 57% of hemodynamically

unstable patients were fluid responsive (Marik 2013). Of importance, a change in blood pressure (or lack thereof) is not a reliable indicator of CO response to a fluid challenge; an assessment of CO (or SV) change should be used instead (Cherpanath 2016). Patients given additional fluid when they are no longer fluid responsive may have detrimental effects of fluid (e.g., pulmonary edema) rather than beneficial effects (increased CO). Although fluid responsiveness should be determined in each patient, it is most critical in patients in whom detrimental fluid effects cannot be tolerated (e.g., those with refractory hypoxemia in the setting of shock).

Fluid responsiveness may be predicted by either static or dynamic markers. Static markers of fluid responsiveness include the cardiac filling pressures CVP and PCWP, whereas dynamic markers of fluid responsiveness include stroke volume variation (SVV), pulse pressure variation (PPV), and IVC collapsibility. Although static markers may help differentiate shock states, they are not reliable predictors of fluid responsiveness. In a study of patients with severe sepsis and septic shock, a CVP less than 8 mm Hg and a PCWP less than 12 mm Hg had fluid responsiveness positive predictive values of 47% and 54%, respectively (Osman 2007). Systematic reviews and meta-analyses suggest that CVP and PCWP should not be used alone as resuscitation parameters (Marik 2013; Marik 2009). In contrast, a meta-analysis showed that PPV and SVV could predict fluid responsiveness with areas under the receiver operating characteristic curve (AUC) of 0.94 and 0.84, respectively, compared with CVP, which had an AUC of 0.55 (Marik 2009).

The dynamic markers PPV, SVV, and IVC collapsibility are based on heart-lung interactions in mechanically ventilated patients. In these patients, a controlled positive pressure breath increases pleural pressure. This increase in intrathoracic pressure leads to a decrease in venous return, decreased right ventricular (RV) preload, and decreased RV SV. Left ventricular preload is subsequently decreased, which may lead to a decrease in LV SV. Patients who are fluid responsive will have relatively large changes in LV SV with positive pressure breaths. This leads to variation in the LV SV between periods with and without positive pressure breaths (Marik 2011). Specific values of PPV and SVV used to predict fluid responsiveness vary by study, specific conditions (e.g., the use of vasopressors), and assessment method or device. In a systematic review, thresholds to predict fluid responsiveness were PPV greater than 12.5% and SVV greater than 11.6% (Marik 2009).

Inferior vena cava collapsibility (also termed *IVC variability* or *IVC distensibility*) is another dynamic marker of fluid responsiveness in mechanically ventilated patients. This method uses echocardiography to visualize the IVC diameter during positive pressure ventilation. With a positive pressure breath, venous return is impaired, and the IVC diameter increases. The change in IVC diameter during inspiration is higher in patients who are fluid responsive than in those who are not fluid responsive. In one study, an IVC diameter change

above 12% predicted fluid responsiveness with a positive predictive value of 93% and a negative predictive value of 92% (Feissel 2004).

Several caveats exist for using these dynamic markers of fluid responsiveness. Use of PPV and SVV has several assumptions, including sinus cardiac rhythm, the absence of significant valvular dysfunction, and intubation and mechanical ventilation without spontaneous breaths. If these assumptions are not fulfilled, PPV and SVV are not reliable in predicting fluid responsiveness. The role of a tidal volume requirement (e.g., 8 mL/kg or more of predicted body weight) as an assumption that must be fulfilled for use of PPV and SVV is controversial and is the subject of ongoing studies. The use of IVC collapsibility also requires intubation and mechanical ventilation without spontaneous breaths and is not conducive to continuous monitoring.

Given these limitations, the passive leg raising (PLR) test may be used to assess fluid responsiveness in patients for whom the assumptions for use of PPV and SVV are not fulfilled, particularly in patients not mechanically ventilated. The PLR test measures the hemodynamic effects of a positional change of the patient's legs. Lifting the patient's legs passively from the horizontal position to a 45-degree angle (or a change in position of the patient's bed) leads to a transfer of blood from the abdominal compartment and lower extremities to the intrathoracic compartment. This increase in venous return may subsequently increase SV and CO (if the patient is fluid responsive). Similar to fluid administration, a patient with a 10%–15% increase in CO after the PLR test is considered fluid responsive. The benefit of the PLR test is that it can be used in spontaneously breathing, nonintubated patients. In addition, PLR does not require fluid administration and can easily be reversed by returning patients to their previous position (Monnet 2015). A caveat to using the PLR test is that a method of determining CO is required to determine response. In addition, intra-abdominal hypertension reduces the ability of PLR to detect fluid responsiveness.

Despite the superiority of dynamic markers to static markers in predicting fluid responsiveness, the incorporation of dynamic markers into a resuscitative strategy that improves patient outcomes in the ICU is still lacking. A randomized controlled trial of patients with septic shock and/or acute respiratory distress syndrome that randomized patients to treatment on the basis of PiCCO (pulse index contour continuous cardiac output)-derived parameters or a control group with parameters obtained by a central venous catheter (e.g., CVP) did not detect a difference in 28-day mortality between study groups (OR 1.00; 95% CI, 0.66–1.52) (Zhang 2015). A pilot study of using protocol-guided assessments of fluid responsiveness after initial resuscitation in patients with septic shock requiring vasopressors found that this approach of using dynamic markers of fluid responsiveness is feasible and appears to be safe, paving the way for larger, outcomes-based trials using this approach (Chen 2015).

Adequate Do₂

Adequate Do₂ must be ensured through monitoring CO, Scvo₂, or Svo₂. A decreased Scvo₂ or Svo₂ shows that tissue oxygen demands are not completely met by Do₂ (and the oxygen extraction ratio has increased). In these cases, a strategy to increase Do₂ (and subsequently increase Scvo₂ or Svo₂) should be used, including fluids to optimize preload, red blood cell transfusion to increase Cao₂, and inotropes to increase CO. Caution must be taken, though, with using Scvo₂ or Svo₂ in isolation as a resuscitation goal. Instead of targeting a specific number or considering the value high or low, it is likely best to interpret CO, Scvo₂, or Svo₂ as either adequate or inadequate (Walley 2011). Adequacy is best determined by assessing end-organ perfusion and lactate concentrations. Strategies of systematically increasing CO to predefined “supranormal” values were not associated with a mortality benefit; hence, this is not recommended. Because Pao₂ does not contribute significantly to Cao₂, it should not be used as a therapeutic target.

Use of lactate clearance and normalization is another method of ensuring adequate Do₂. Lactate clearance suggests improvement in global tissue perfusion and is associated with a decreased mortality rate in patients with sepsis (Nguyen 2004). Lactate normalization is also a strong independent predictor of survival in patients with sepsis and is perhaps better than lactate clearance (Puskarich 2013). A protocol-based approach to resuscitating patients with severe sepsis or septic shock targeting a lactate clearance of at least 10% was noninferior to an approach targeting an Scvo₂ above 70% (Jones 2010). The combination of lactate clearance and Scvo₂ above 70% as resuscitation goals in patients with sepsis was associated with improved mortality (after multivariable adjustment) compared with optional Scvo₂ and no lactate monitoring (Jansen 2010). Targeting lactate clearance or normalization is an attractive end point because it does not require invasive hemodynamic monitoring. If available, use of both lactate clearance and Scvo₂ (or Svo₂) may best ensure adequate Do₂.

FLUIDS AND VASOACTIVE AGENTS USED TO TREAT SHOCK

Patients with circulatory shock are typically treated with fluids, vasoactive agents (vasopressors or vasodilators), or inotropes. Therapeutic selection is based on an assessment of resuscitation parameters matched to the pharmacodynamic effects of the agent(s) that will best augment the aberrant parameter(s).

Fluids

Resuscitation fluids are given to about one in four patients in the ICU (Hammond 2015). Ideally, fluids are only given to patients who are predicted or determined to be fluid responsive and are administered with a fluid challenge technique.

The optimal fluid for resuscitating a patient with circulatory shock, though, remains the subject of much debate.

The SAFE study found no difference in 28-day mortality between treatment with 0.9% sodium chloride and treatment with 4% albumin (20.9% vs. 21.1%, $p=0.87$) (Finfer 2004). As a result, crystalloids are preferred for initial resuscitation, given that they cost less than albumin. However, the allocated study fluid was used for all fluid resuscitation in the ICU until death, discharge, or 28 days after randomization, not just during initial resuscitation. A meta-analysis of albumin compared with alternative fluids for resuscitation in patients with sepsis found an association between albumin use and lower mortality (OR 0.82; 95% CI, 0.67–1.0). The benefit of albumin was retained when the analysis was restricted to crystalloids as the comparator (OR 0.78; 95% CI, 0.62–0.99) (Delaney 2011). These data should be considered hypothesis generating because many of the included studies had poor methodological quality, and when a random-effects model was used, the results for the overall analysis were not statistically significant. Several studies of albumin as the initial resuscitation fluid for patients with shock are ongoing.

Hydroxyethyl starch solutions should not be used for resuscitation in the ICU. A systematic review and meta-analysis that analyzed only trials without documented investigator misconduct found an association between hydroxyethyl starch use and increased patient mortality (risk ratio 1.09; 95% CI, 1.02–1.17), increased renal failure (risk ratio 1.27; 95% CI, 1.09–1.47), and need for renal replacement therapy (risk ratio 1.32; 95% CI, 1.15–1.50) (Zarychanski 2013).

The type of crystalloid fluid (Table 3-2) to use for resuscitation is of increasing interest. Administration of chloride-rich fluids may lead to afferent renal arteriole vasoconstriction (leading to a decrease in renal perfusion and kidney injury) and may cause a metabolic acidosis by lowering the strong ion difference (Yunos 2010). As such, crystalloids that better approximate the electrolyte composition of plasma have been evaluated.

In observational studies, the use of chloride-poor fluids has been associated with a significantly lower incidence of acute kidney injury, use of renal replacement therapy, and risk of major postoperative complications (Shaw 2012; Yunos 2012). However, in a large, double-blind, cluster randomized trial comparing a balanced crystalloid solution (Plasma-Lyte) with 0.9% sodium chloride for treatment of all patients requiring crystalloid fluid therapy, the balanced crystalloid solution group had no lower risk of acute kidney injury (9.6% vs. 9.2%; RR 1.04; 95% CI, 0.80–1.36). In addition, there was no difference between groups in the use of renal replacement therapy (RR 0.96; 95% CI, 0.62–1.50) or hospital mortality (RR 0.88; 95% CI, 0.67–1.17) (Young 2015). Critiques of this study include the use of study fluid for all crystalloid fluid therapy needs (not just as a resuscitation fluid for circulatory shock), significant heterogeneity ($p=0.05$) of the treatment's effect on acute kidney injury by specific ICU study site (suggesting

Table 3-2. Sodium and Chloride Content of Commonly Used Resuscitative Fluids

Fluid	Sodium (mmol/L)	Chloride (mmol/L)
Chloride rich ^a		
0.9% sodium chloride	154	154
4%–5% albumin	130–160 ^b	0–128 ^b
Chloride poor ^a		
Lactated Ringer solution	131	111
Plasma-Lyte 148	140	98
Normosol-R	140	98
20%–25% albumin	130–160 ^b	0–19 ^b

^aDistinction of “chloride rich” and “chloride poor” is based on chloride content above or below 120 mmol/L.

^bDiffers according to manufacturer because of differences in buffer type (e.g., sodium bicarbonate or sodium chloride) and amount used. Reported chloride content is 128 mmol/L for 4% Albumex and 19 mmol/L for 20% Albumex (CSL Bioplasma; products used in Australia/New Zealand); this led to the distinction of “chloride rich” and “chloride poor” for 4%–5% albumin and 20%–25% albumin, respectively. However, 5% and 25% Flexbumin (Baxter; products available in the United States) do not contain chloride.

Information from: Guidet B, Soni N, Della Roca G, et al. A balanced view of balanced solutions. *Crit Care* 2010;14:325; Frazee EN, Leedahl DD, Kashani KB. Key controversies in colloid and crystalloid fluid utilization. *Hosp Pharm* 2015;50:446-53; and Yunus NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566-72.

center-related treatment differences), and debatable widespread external validity in light of the predominantly surgical population and relatively low severity of patient illness. A better understanding of the efficacy of balanced salt solutions is needed because these therapies are not without risk. They may lead to hyponatremia (with lactated Ringer solution) or cardiotoxicity (with acetate-containing solutions) when administered in large volumes (Myburgh 2013). At this time, the role of balanced crystalloid solutions for resuscitating patients with circulatory shock is unclear.

Vasoactive Agents and Inotropes

Vasoactive agents and inotropes are typically classified according to their primary effects, but an individual agent may have many effects, resulting in differences in pressure and flow (Table 3-3) (Hollenberg 2011). Once the decision to initiate a vasoactive agent is made, selecting a vasoactive agent or inotrope is largely based on choosing the agent that best achieves the desired pharmacodynamic effect (e.g., increase in SVR or increase in CO). In most shock syndromes, limited literature exists to guide optimal vasoactive agent selection. Vasopressor agents are the most common agents used in the salvage and optimization treatment stages, and they are indicated if hypotension is refractory to fluid administration or in severe hypotension while fluids are being administered. Although objective criteria exist, a lack of fluid responsiveness is often assessed subjectively

in practice. In addition, if a patient is severely hypotensive, vasopressors may be initiated (together with additional fluid administration), even if a patient is still fluid responsive, to ensure adequate end-organ perfusion. Because there are no definitive criteria for when vasopressors should be initiated, bedside clinicians often need to make a patient-specific assessment and decision.

The largest comparative study of vasopressors for the treatment of circulatory shock included 1679 patients requiring vasopressors for treatment of any shock type. Enrolled patients were allocated to either blinded norepinephrine or dopamine. There was no difference in 28-day mortality between patients receiving dopamine and those receiving norepinephrine (52.5% vs. 48.5%, $p=0.10$), but patients receiving dopamine more commonly developed an arrhythmia (24.1% vs. 12.4%, $p<0.001$), required open-label norepinephrine (26% vs. 20%, $p<0.001$), and required more days with vasopressor support (De Backer 2010). Although norepinephrine may not improve mortality compared with dopamine, it is safer and more effective. Another multicenter randomized trial comparing norepinephrine with epinephrine for patients with undifferentiated shock found no difference between agents in the time to achieving a goal MAP (median 40 hours vs. 35.1 hours, $p=0.26$) or median number of vasopressor-free days at day 28 (25.4 days vs. 26.0 days, $p=0.31$) (Myburgh 2008). Patients allocated to epinephrine had higher heart rates and lactic acid concentrations on the first study

Patient Care Scenario

A 49-year-old man (height 69 inches, weight 71 kg) with a medical history of a motor vehicle accident complicated by quadriplegia and neurogenic bladder presents with altered mental status and hypotension likely secondary to a UTI complicated by sepsis. After receiving initial fluid resuscitation and appropriate antibiotics, he remains hemodynamically unstable, requiring initiation of norepinephrine, and is intubated for airway protection. Pertinent clinical values are as follows: blood pressure 98/49 mm Hg (MAP 65 mm Hg) on norepinephrine 10 mcg/minute,

heart rate 112 beats/minute in sinus rhythm, respiratory rate 14 breaths/minute (ventilator rate 14 breaths/minute, tidal volume 575 mL), and CVP 9 mm Hg. Current laboratory values include Na 150 mEq/L, K 4.9 mEq/L, Cl 113 mEq/L, BUN 40 g/dL, and SCr 1.4 mg/dL (baseline 0.5 mg/dL). Analysis of the arterial waveform shows a PPV of about 16%. First, determine whether the patient is fluid responsive, and if applicable, recommend the best fluid type for resuscitation in this patient.

ANSWER

First, assess the patient's need for additional fluid, which is evaluated according to markers of fluid responsiveness including static markers (CVP or PCWP) and dynamic markers (IVC collapsibility, PPV, SVV, or CO or CI increase on PLR test). Dynamic markers better predict fluid responsiveness, though there are important caveats to their use. PPV requires the patient to be in sinus rhythm, without significant valvular dysfunction, intubated and ventilated without spontaneous breaths, and (typically) receiving a tidal volume of 8 mL/kg or more of predicted body weight. Because these criteria are met for this patient, PPV is the most appropriate marker to assess fluid responsiveness. The PPV value is greater than 13%; therefore, the patient is predicted to be fluid responsive.

After determining that the patient is likely fluid responsive, next determine the best fluid to administer.

Crystalloids are preferred to colloids such as albumin and hydroxyethyl starch for fluid resuscitation in the ICU because studies did not find a difference in efficacy between crystalloids and colloids, whereas colloids are associated with higher cost and increased adverse events (e.g., hydroxyethyl starch). The optimal crystalloid for fluid resuscitation is still unknown. Nonrandomized data suggest that administration of chloride-rich fluids such as 0.9% sodium chloride leads to acute kidney injury compared with chloride-poor fluids (e.g., lactated Ringer solution). However, randomized controlled trials have found no difference in acute kidney injury between the two types of crystalloids. Despite the lack of consensus, in this patient, who already has elevated serum sodium and chloride concentrations, a fluid that is more balanced in both sodium and chloride such as lactated Ringer solution would be best.

1. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2011;1:1.
2. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs. chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566-72.
3. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs. saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA* 2015;315:1701-10.

day (but not on subsequent days) and were more often withdrawn from the study by the treating clinician (12.9% vs. 2.8%, $p=0.002$). Epinephrine offers no efficacy benefits over norepinephrine and is associated with an increased incidence of adverse effects (at least initially). Although norepinephrine may be considered as the first-line vasoactive medication of choice in most shock types, the desired therapeutic effects of the initial vasoactive agent must still be considered.

SHOCK STATE-SPECIFIC TREATMENT

Hypovolemic Shock

Although commonly associated with trauma, hypovolemic shock can occur in other clinical scenarios (e.g., acute GI bleeding, surgical, obstetric, pharmacologic toxicity). Hemorrhagic shock occurs when intravascular volume loss impairs Do_2 ; it can be categorized as either whole blood loss (from an open wound or into a body compartment) or plasma loss (into the extravascular space). The mainstays of hypovolemic shock treatment are to address the underlying cause of

intravascular volume loss and replace the lost intravascular contents. In addition, methods to avoid or reduce the severity of traumatic coagulopathy, which results from a combination of bleeding-induced shock, tissue injury-related thrombin-thrombomodulin-complex generation, and activation of anticoagulant and fibrinolytic pathways, should be used (Rossaint 2016).

Isotonic crystalloid fluids are the initial fluid of choice. In patients with severe head trauma, consideration should be given to avoid lactated Ringer solution (a fluid that is relatively hypotonic) to minimize fluid shifts into the cerebral tissue. Although theoretically beneficial, administration of hypertonic or hyperoncotic solutions in patients with traumatic hypovolemic shock has not been associated with improved patient survival compared with 0.9% sodium chloride (Bulger 2011). Albumin is not recommended as an initial resuscitation fluid in patients with traumatic brain injury, particularly patients with severe brain injury (Glasgow Coma Scale scores of 3–8), because it has been associated with increased mortality in these patients (SAFE Study Investigators 2007). A target

Table 3-3. Vasoactive Agent Pharmacology and Pharmacodynamic Effects

	DA	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Vasopressors										
Dopamine ^a	+++++	+++	++++	++		↑	↔ or ↑	↑	↔ or ↑	↔ or ↑
Epinephrine ^a		++++	++++	+++		↑	↔ or ↑	↑	↑	↑
Norepinephrine ^a		+++++	+++	++		↔ or ↑	↔ or ↑	↔ or ↑	↑	↑
Phenylephrine		+++++				↔ or ↓	↔ or ↑	↔ or ↓	↑	↑
Vasopressin	N/A	N/A	N/A	N/A	V ₁ R and V ₂ R agonism	↔ or ↓	↔ or ↑	↔ or ↓	↑	↔ or ↓
Inotropes										
Dobutamine		+	++++	++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Levosimendan ^b	N/A	N/A	N/A	N/A	Ca ²⁺ sensitization and K _{ATP} activation	↔	↔ or ↓	↑	↓	↓
Milrinone ^c	N/A	N/A	N/A	N/A	PDE3 inhibition	↔ or ↑	↔ or ↓	↑	↓	↓
Vasodilators										
Nitroglycerin	N/A	N/A	N/A	N/A	cGMP	↔ or ↑	↓	↔ or ↑	↔ or ↓	↔ or ↓
Nitroprusside	N/A	N/A	N/A	N/A	cGMP	↔ or ↑	↓	↔ or ↑	↓	↓
Nesiritide	N/A	N/A	N/A	N/A	cAMP	↔ or ↑	↔ or ↓	↔ or ↑	↔ or ↓	↓
Nitric oxide (inhaled)	N/A	N/A	N/A	N/A	cGMP	N/A	↔	↔ or ↑	↔	↓
Epoprostenol (aerosolized)	N/A	N/A	N/A	N/A	cAMP	N/A	↔	↔ or ↑	↔ or ↓	↓

^aHigh doses associated with increasing α_1 activity.

^bNot available for commercial use in the United States.

^cNormal half-life is 2.5 hr but is eliminated renally. Loading dose rarely used in routine management.

↑ = increases; ↓ = decreases; ↔ = no (or minimal) change.

Ca²⁺ = calcium; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DA = dopaminergic; K_{ATP} = adenosine triphosphate-sensitive potassium channels; N/A = not applicable; PDE3 = phosphodiesterase type 3; V₁R = vasopressin type 1 receptor; V₂R = vasopressin type 2 receptor.

Modified with permission from: Abel EE. Cardiovascular critical care. In: Abel EE, Bauer SR, Benken ST, et al. Critical Care Pharmacy Preparatory Review and Recertification Course. American College of Clinical Pharmacy, Lenexa, KS, 2016:1-233-87.

SBP of 80–90 mm Hg (greater than 80 mm Hg in patients with severe traumatic brain injury) and restricted volume replacement strategy should be used until major bleeding has been stopped (Rossaint 2016; Cecconi 2014). Vasopressors should only be used as a temporizing measure in profound hypotension despite ongoing volume resuscitation.

Blood product administration may also be indicated. Compared with a liberal packed red blood cell (PRBC) transfusion threshold of hemoglobin concentration less than 10 g/dL, a restrictive transfusion threshold of hemoglobin concentration less than 7 g/dL was associated with a similar incidence of favorable outcome with fewer thrombotic events in patients with traumatic brain injury (Robertson

2014) and lower mortality, further bleeding, and adverse events in patients with upper GI bleeding (Villanueva 2013). A target hemoglobin concentration of 7–9 g/dL has been recommended (Rossaint 2016). Treatment of the acutely bleeding patient should prioritize correction of hypothermia, acidemia, and hypocalcemia because they exacerbate acute traumatic coagulopathy. Blood component therapy, consisting of transfusion of plasma, platelets, and PRBCs, remains the standard of therapy for the treatment of coagulopathy. The optimal ratio of plasma/platelets/PRBCs is unclear, but a recent multicenter, randomized trial that compared a balanced 1:1:1 damage control resuscitation transfusion strategy with a ratio of 1:1:2 in adult trauma patients found

no significant differences in 24-hour or 30-day mortality. However, hemostasis was achieved in more patients randomized to the 1:1:1 arm, highlighting the importance of early platelet transfusion (Holcomb 2015). European guidelines, though, recommend transfusion of plasma and PRBCs in a ratio of at least 1:2, with platelet transfusion based on platelet count (Rossaint 2016).

Pharmacologic management of bleeding is also important in patients with hemorrhagic shock, with a focus on antifibrinolytic therapy and reversal of antithrombotic agents. In a randomized controlled trial of 20,211 adult trauma patients with significant hemorrhage or considered at risk of significant hemorrhage, tranexamic acid dosed as a 1-g bolus over 10 minutes followed by a 1-g infusion over 8 hours was associated with reduced 28-day all-cause mortality compared with placebo (RR 0.91; 95% CI, 0.85–0.97) and mortality caused by bleeding (RR 0.85; 95% CI, 0.76–0.96) (CRASH-2 trial collaborators 2010). Administration of tranexamic acid as soon as possible is strongly recommended in trauma patients with hemorrhage or at risk of significant hemorrhage (Rossaint 2016). Subgroup analysis of the CRASH-2 study showed that the most benefit is derived if tranexamic acid is administered within 3 hours from injury (CRASH-2 collaborators 2011).

Cardiogenic Shock

Cardiogenic shock is different from other forms of shock; hypotension and end-organ hypoperfusion result primarily from reduced CO because of myocardial dysfunction, specifically defined as a reduced CI (CI less than 1.8 L/minute/m²) in the presence of adequate cardiac filling pressures (PCWP greater than 18 mm Hg) (Thiele 2015). The most common causes of cardiogenic shock, making up almost 80% of cases, are acute ST-segment elevation MI and non-ST-segment elevation MI with LV failure. Other causes include acute decompensation of heart failure and valvular disease.

Any direct ischemic or mechanical injury can lead to reduced CO and result in cardiogenic shock. Reduced CO triggers several compensatory mechanisms. These include the release of catecholamines and activation of the renin-angiotensin-aldosterone (RAAS) system. Release of catecholamines causes vasoconstriction, inotropy, and chronotropy. Activation of the RAAS system leads to increased production of angiotensin II, causing vasoconstriction, and aldosterone release, causing salt and water retention. Together, these compensatory responses increase preload and afterload and decrease coronary perfusion, which all increase myocardial demand, further reducing CO and exacerbating cardiogenic shock.

As with other types of shock, early management of cardiogenic shock includes initial resuscitation with fluids and vasoactive agents as indicated. Use of fluids and vasoactive agents in cardiogenic shock can be difficult to assess because most patients have elevated PCWP and SVR and may not respond to fluids and vasoactive agents. A PAC may be useful to guide therapy on the basis of hemodynamic parameters such as CO/CI, PCWP, and SVR. Figure 3-2 shows how therapy should be managed according to the hemodynamic parameters in the setting of cardiogenic shock.

When vasopressor support is needed to maintain blood pressure in cardiogenic shock, the treatment of choice is norepinephrine. Although data are limited on the use of vasopressors in cardiogenic shock, the trial that compared the use of norepinephrine and dopamine in the management of all shock types included a predefined subgroup of 280 patients with cardiogenic shock (De Backer 2010). In patients with cardiogenic shock, dopamine was associated with a significantly higher 28-day mortality than norepinephrine (p=0.03), though the treatment effect did not differ among shock subgroups (interaction p=0.87).

When fluids or vasopressors cannot maintain perfusion in cardiogenic shock, inotropes are an appropriate next step.

	PCWP < 18 mm Hg	PCWP > 18 mm Hg
CI > 2.2 L/min/m ²	Subset I: Warm and Dry Treatment: Medical optimization	Subset II: Warm and Wet Treatment: IV diuretics ± vasodilators
CI < 2.2 L/min/m ²	Subset III: Cold and Dry Treatment: IV fluids until PCWP 15–18 mm Hg IV dobutamine Consider IV vasodilator if MAP tolerates IV vasopressor if hypotensive	Subset IV: Cold and Wet Treatment: IV diuretics + IV dobutamine Consider IV vasodilator if MAP tolerates IV vasopressor if hypotensive

Figure 3-2. Treatment of cardiogenic shock according to hemodynamic profile.

CI = cardiac index; IV = intravenous; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure.

Information from: Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA 2002;287:628-40.

Inotropes are only indicated in cardiogenic shock when there is evidence of reduced CO despite adequate intravascular volume. The first-line inotrope in patients with cardiogenic shock is dobutamine. The successful combination of norepinephrine and dobutamine in patients with cardiogenic shock was shown in the previously mentioned trial, with 19.4% of all patients receiving norepinephrine also receiving dobutamine (De Backer 2010). The benefit of dobutamine was also evaluated in a small study of 30 patients with cardiogenic shock who were randomized to receive either the combination of norepinephrine and dobutamine or epinephrine alone (Levy 2011). Compared with patients who received epinephrine, patients who received norepinephrine and dobutamine had lower rates of lactic acidosis, tachycardia, and arrhythmias. Although dobutamine is preferred in cardiogenic shock, alternative inotropes such as levosimendan and milrinone may be useful in special populations. For instance, levosimendan may be preferred in patients with a history of chronic heart failure, particularly those receiving β -blockers, but it is not currently available for use in the United States. In addition, compared with dobutamine, levosimendan and milrinone may be favored for patients with pulmonary hypertension (PH) because these agents decrease cardiac filling pressures and pulmonary vascular resistance (PVR).

Inotrope and vasopressor support alone may not be sufficient to maintain adequate tissue perfusion in a patient with cardiogenic shock. In these instances, mechanical support is recommended to help improve hemodynamics, maintain perfusion, and reduce myocardial demand. Current guidelines recommend the use of intra-aortic balloon pump (IABP) treatment for patients who do not quickly respond to pharmacologic treatment such as inotropes (O'Gara 2013). Intra-aortic balloon pump treatment improves diastolic pressure, while reducing afterload, to decrease myocardial demand without negatively affecting coronary perfusion. However, a randomized trial of 600 patients with cardiogenic shock secondary to acute MI undergoing early revascularization found no difference in 30-day mortality with either IABP or conventional treatment (39.7 vs. 41.3%, $p=0.69$) (Thiele 2012). In addition, there are concerns with the use of IABP, including access site bleeding, limb ischemia, and thrombocytopenia. In patients not responding to IABP or with refractory cardiogenic shock, guidelines recommend the use of LV assist device or extracorporeal membrane oxygenation (O'Gara 2013). Additional details on mechanical support options are provided in the Advanced Heart Failure chapter.

The most important treatment for cardiogenic shock secondary to acute MI is early revascularization by either percutaneous coronary intervention or coronary artery bypass grafting. Although a study of about 300 patients with cardiogenic shock secondary to acute MI randomized patients to receive either early revascularization within 18 hours or medical therapy (including thrombolytics) found no difference in 30-day mortality, there was a 9% absolute reduction in 30-day

mortality in patients randomized to receive early revascularization ($p=0.11$) and a 13% absolute reduction in 6-month and 1-year mortality, supporting the use of early revascularization ($p=0.03$) (Hochman 1999). Early revascularization, which is strongly recommended in the current guidelines, should be prioritized (O'Gara 2013).

Obstructive Shock

Obstructive shock is similar to cardiogenic shock; in both, the major hemodynamic dysfunction is impaired CO, but the dysfunction occurs as a result of extracardiac obstruction to flow in the cardiovascular system. The source of extracardiac obstruction may be either impaired diastolic filling (e.g., cardiac tamponade, tension pneumothorax, or constrictive pericarditis) or impaired systolic contraction (e.g., massive pulmonary embolism [PE], acute or chronic PH, or aortic dissection). The specific pathophysiologic derangements depend on the underlying cause of the extracardiac obstruction. In impaired diastolic filling, RV preload is significantly decreased because of the inhibition of venous return, whereas in impaired systolic function, ventricular afterload is acutely increased, leading to biventricular failure.

Treatment of obstructive shock primarily focuses on correcting the underlying cause, with fluids and vasopressors used as temporizing measures to increase tissue perfusion. Intravenous fluids (typically crystalloids) are generally recommended, but they may be ineffective at improving CO in patients with cardiac tamponade (Kerber 1982). Even so, fluid administration is often recommended in cardiac tamponade because of impaired venous return. Initial fluid administration improves CO in patients with massive PE, but care should be taken because excessive fluid administration can lead to further RV dilation and impaired LV contractility from worsened septal shifting and decreased LV filling (because of intraventricular dependence) (Greyson 2008). Optimizing fluids in patients with acute or chronic PH is challenging. Patients with signs of intravascular volume depletion may require fluids, whereas others may require diuretics to reduce RV dilation and improve LV filling (even in the setting of vasoactive medication administration) (Hoepfer 2011). Hence, determining the etiology of the obstructive shock state is paramount.

Vasopressors should be initiated to increase MAP and maintain an adequate perfusion pressure when patients have signs of hypoperfusion. This is particularly important in massive PE because adequate right coronary artery perfusion is of greatest importance to prevent/reduce RV free wall ischemia. Caution must be taken because catecholamine vasopressors may increase PVR (which may worsen RV dysfunction). Inotropes may increase RV CO in massive PE or acute or chronic PH, but they are likely ineffective in tamponade. Inhaled nitric oxide or aerosolized prostacyclin therapy may be effective in decreasing RV afterload in acute or chronic PH (Dzierba 2014), but neither therapy is likely effective for massive PE or cardiac tamponade.

Definitive treatment of the extracardiac obstruction is paramount. Mechanical therapies are the primary treatments for patients with impaired diastolic dysfunction; patients with cardiac tamponade should be evaluated for pericardiocentesis or surgical evacuation, whereas those with tension pneumothorax should be considered for needle decompression and potential chest tube thoracostomy. Patients with circulatory shock secondary to PE should undergo embolism dissolution (with thrombolytic therapy) or removal (with surgical or catheter thrombectomy).

Thrombolytic agents can lead to rapid PE dissolution and a subsequent decrease in PVR, but they may also cause bleeding. Thrombolytics do not decrease mortality in unselected patients with PE compared with heparin alone, but they may improve outcomes in patients with an increased risk of death (Wan 2004). Early PE-related mortality risk stratification is necessary to guide thrombolytic therapy administration. High-risk PE (or “massive PE”) is not defined by clot burden, but by acute PE causing hemodynamic changes (hypotension, pulselessness, or bradycardia). Intermediate-risk PE (or “submassive PE”) is an acute PE without systemic hypotension but with either RV dysfunction or myocardial necrosis. Low-risk PE is an acute PE not meeting the definitions for high- or intermediate-risk PE. A meta-analysis found that thrombolytics were associated with a lower rate of recurrent PE or death than heparin alone in patients with massive PE (OR 0.45; 95% CI, 0.22–0.92) (Wan 2004). Thrombolytics are recommended for patients with massive PE and an acceptable risk of bleeding complications (Kearon 2016; Jaff 2011).

Unlike massive PE, clinical controversy exists regarding the risk-benefit profile of systemic thrombolytic administration for patients with submassive PE. In a 2002 study, adding alteplase 100 mg infused over 2 hours to heparin compared with adding heparin alone was associated with a lower rate of death or clinical deterioration requiring an escalation in treatment (11.0% vs. 24.6%, $p=0.006$). This result was driven by more patients in the heparin-alone arm who received secondary thrombolytics (23.2% vs. 7.6%, $p=0.001$), which may have been influenced by investigators’ ability to break the blinding of treatment allocation in the study (Konstantinides 2002). A more recent study of patients with submassive PE (fulfilling both RV dysfunction and myocardial necrosis criteria) randomized patients to weight-based tenecteplase plus heparin or heparin alone. Between randomization and day 7, patients allocated to tenecteplase less commonly experienced death or hemodynamic decompensation (2.6% vs. 5.6%, $p=0.02$; number needed to treat 33 patients) but more commonly experienced major extracranial bleeding (6.3% vs. 1.2%, $p<0.001$; number needed to harm = 19 patients) and stroke (2.4% vs. 0.2%, $p=0.003$; number needed to harm = 45 patients). The difference in stroke incidence was driven by a higher incidence of hemorrhagic stroke in the tenecteplase arm (2.0% vs. 0.2%, $p=0.01$, number needed to harm = 55 patients) (Meyer 2014). The results call into question the risk-benefit profile of

tenecteplase for submassive PE. The most recent guidelines recommend against systemically administered thrombolytic therapy in most patients with PE not associated with hypotension (Kearon 2016). Ultrasound-assisted catheter-directed thrombolysis is an emerging treatment approach, but systemic thrombolytic therapy is currently recommended over a catheter-directed approach (Kearon 2016). The risks and benefits of systemic thrombolytics are best determined on a case-by-case basis by the bedside clinician. In extreme circumstances (e.g., massive PE with impending cardiac arrest), even the presence of strong risk factors for bleeding may not preclude some clinicians from administering thrombolytics because of the potential for benefit from the therapy. In these settings, even the “contraindications” noted in the product labeling, other than active internal bleeding, may be considered “relative contraindications” by some clinicians for thrombolytic administration.

Patients with a massive or submassive PE who (1) have an unacceptably high risk of bleeding from thrombolytic administration, (2) remain unstable despite thrombolytic administration, or (3) have shock likely to cause death within hours (before the onset of systemic thrombolytics) should be considered for surgical embolectomy or catheter thrombectomy. Unless contraindicated, all patients should also receive a parenteral anticoagulant. Intravenous unfractionated heparin is recommended over alternative agents for patients in whom thrombolytic therapy is being considered or planned. If anticoagulation is contraindicated, an IVC filter should be placed.

Vasodilatory/Distributive Shock

Vasodilatory/distributive shock is the most commonly encountered type of shock, with about 66% of patients requiring vasoactive drugs having this shock type (De Backer 2010). *Vasodilatory shock* is a broad term that describes tissue hypoperfusion secondary to a decrease in SVR (or hypoperfusion despite a normal or elevated CO), whereas *distributive shock* is technically a subset of vasodilatory shock that describes maldistribution of blood flow at the level of microcirculation (shunting) or at the organ level, though the terms are often used interchangeably. Septic shock is the most common cause, but this shock type may also occur in other conditions, including immune-mediated (“anaphylactic”) and nonimmunologic (“anaphylactoid”) reactions, neurogenic shock (classically secondary to spinal cord injury), intoxication, peridural or epidural infusion, adrenal insufficiency (Addisonian crisis), and thyroid insufficiency (myxedema coma) or as a component of ischemia-reperfusion injury (e.g., after cardiac arrest or cardiopulmonary bypass). Vasodilatory shock occurs because of a failure of the vascular smooth muscle cells to constrict, whether from a failure of vasoconstriction methods or the inappropriate activation of vasodilatory mechanisms. Profound vasodilation leads to ineffective circulating plasma volume (either from venodilation or from fluid shifts because of increased

vascular permeability) and resultant decreases in cardiac preload and CO. Patients with septic shock may also have inadequate CO after fluid resuscitation because of mechanisms that are poorly understood. Given these findings, fluids, vasopressors, and inotropes are all considerations for use in a patient with vasodilatory shock.

The underlying cause of the shock state must quickly be addressed when resuscitation is initiated. Patients with septic shock should be treated according to the Surviving Sepsis Campaign management bundle (Box 3-1), including administration of antimicrobials with activity against all likely pathogens within 1 hour of disease recognition (Dellinger 2013). The potential offending agent should be discontinued and, if possible, clearance augmented for patients with immune-mediated shock. The treatment goals and end points of resuscitation are generally similar to those outlined previously, though in acute spinal cord injury, an initial MAP goal of 85–90 mm Hg is recommended (Walters 2013).

Because sepsis was previously covered in this series, treatment will only be briefly discussed. New definitions for

sepsis have been developed and recently published. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer 2016). Organ dysfunction can be identified as an acute change in the total sequential organ failure assessment (SOFA) score by 2 points or more after the infection. This definition is useful to predict poor outcomes secondary to sepsis, but it is not sensitive enough to identify patients with infection or sepsis. A prompt identification tool (quick SOFA [qSOFA]) for recognizing patients outside the ICU at risk of decompensation has also been proposed, which includes alteration in mental status, SBP of 100 mm Hg or less, and respiratory rate of 22 breaths/minute or greater. The presence of two or more qSOFA criteria should prompt clinicians to further determine whether the patient has infection (Vincent 2016). Septic shock is considered a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality substantially. Patients with septic shock can be identified as having hypotension requiring vasopressors to maintain a MAP of 65 mm Hg or greater and a serum lactate concentration greater than 2 mmol/L, despite adequate volume resuscitation. The term *severe sepsis* was removed from the new definition and replaced with simply *sepsis*. These definitions will likely shift patient identification and terminology in clinical practice, particularly for patient inclusion in studies.

The initial resuscitation agent for a patient with vasodilatory shock is intravenous fluids, which restore effective circulating volume. Crystalloids are typically the initial fluid of choice and should be given until the patient is no longer fluid responsive. Patients with sepsis should be given a fluid challenge (typically 30 mL/kg of crystalloid) as quickly as possible. If the blood pressure reading in a patient with sepsis does not improve after the fluid challenge or if the initial serum lactate concentration is above 4 mmol/L, quantitative resuscitation should be initiated. This strategy includes using intensive monitoring, setting goals for hemodynamic support, and using therapies to achieve those goals (see [Online Appendix](#)). Of importance, CVP and ScvO₂ goals are not mandatory components of quantitative resuscitation for a patient with sepsis or septic shock (Angus 2015).

Norepinephrine is generally considered the first-line vasopressor because it can increase SVR without decreasing CO and has been associated with a lower mortality than dopamine in patients with septic shock (De Backer 2012). Epinephrine is typically used for patients with immune-mediated shock out of convention, but no compelling data support the use of epinephrine over alternative agents (Sampson 2005). In addition, no strong data support the use of concomitant histamine-1 and histamine-2 receptor antagonists and corticosteroids in the management of immune-mediated shock (Sampson 2005). In neurogenic shock, agents with combined vasoconstrictive and inotropic properties (e.g., norepinephrine, dopamine, epinephrine) are preferred. High-dose corticosteroids are not recommended for patients with acute spinal cord

Box 3-1. Surviving Sepsis Campaign Management Bundle^a

Accomplished within 3 hr of presentation^b:

1. Measure lactate concentration
2. Obtain blood cultures before administering antibiotics
3. Administer broad-spectrum antibiotics
4. Administer crystalloid 30 mL/kg for hypotension or lactate \geq 4 mmol/L

If septic shock present,^c additional measures to be accomplished within 6 hr of presentation^b:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain MAP \geq 65 mm Hg)
6. If persistent arterial hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial was lactate \geq 4 mmol/L, reassess volume status and tissue perfusion, and document findings^d
7. Remeasure lactate if the initial lactate concentration was elevated

^aApplies to all patients with severe sepsis and septic shock (using 2001 consensus definition).

^bTime of presentation is defined as the time of triage in the ED or, if the patient is located in another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

^cSeptic shock defined as hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or SBP decrease > 40 mm Hg from known baseline) or lactate concentration \geq 4 mmol/L.

^dTo meet the requirements, one of the following must be documented: (1) a focused examination by a licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, heart rate, and skin findings; or (2) any two of the following: measure CVP, measure ScvO₂, bedside cardiovascular ultrasonography, or dynamic assessment of fluid responsiveness with PLR or fluid challenge.

Information from: Surviving Sepsis Campaign. [Updated Bundles in Response to New Evidence](#) [homepage on the Internet].

injury (Walters 2013). For recommendations for the treatment of patients with sepsis, see the [Online Appendix](#).

CONCLUSION

Patients with circulatory shock are commonly encountered in the ICU. Clinical pharmacists can play an important role in designing an optimal treatment plan. To design the best individualized therapeutic plan, the clinician must have a thorough understanding of the pathophysiology, monitoring, and treatment of circulatory shock.

Practice Points

Clinical pharmacists face many challenges in their efforts to optimize pharmacotherapy for their patients with circulatory shock. A thorough understanding of the pathophysiology, monitoring, and treatment of circulatory shock is imperative for the clinical pharmacist. Monitoring techniques and optimal resuscitation parameters continue to evolve, leading to new treatment approaches. As a result, guidelines/recommendations, new uses for existing medications, and safety issues continue to change, as summarized in the following:

- Although blood pressure is typically used to identify a patient with shock, clinical signs of tissue hypoperfusion must also be considered
- Circulatory shock is classified into one of four etiology mechanisms according to hemodynamic profile: (1) hypovolemic, (2) cardiogenic, (3) obstructive, and (4) vasodilatory/distributive; mixed picture may exist
- Dynamic markers of fluid responsiveness should be used instead of static markers (when assumptions are fulfilled)
- CO, Scvo₂, or Svo₂ should be assessed as either adequate or inadequate by assessing end-organ perfusion and lactate concentrations; if inadequate, interventions to raise Do₂ should be made
- Initial resuscitation efforts should focus on treating the underlying cause of the shock type with concomitant supportive care
- Crystalloids are the first-line resuscitation fluid type
- In most shock states, norepinephrine is the initial vasopressor of choice
- Selection of the optimal vasoactive agent is largely based on choosing the agent that best achieves the desired pharmacodynamics effect
- The mainstays of hypovolemic shock treatment are to address the underlying cause of intravascular volume loss (e.g., surgical hemostasis) and replace the lost intravascular contents
- Inotropes are only indicated in patients with cardiogenic shock when there is evidence of reduced CO despite adequate intravascular volume, as evidenced by elevated PCWP or CVP
- Thrombolytic therapy should be pursued in patients with high risk PE, but routine use in patients with intermediate risk PE remains controversial
- Patients with septic shock should be treated initially according to the Surviving Sepsis Campaign management bundle, with subsequent therapies directed by the Surviving Sepsis Campaign guideline recommendations

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Self-Assessment Questions

41. A 62-year-old woman is admitted to the cardiac surgery ICU after mitral valve replacement. On postoperative day 5, she develops increasing fraction of inspired oxygen (F_{iO_2}) requirements, increased sputum production, temperature of 101.8°F (38.8°C), and a new left lower lobe opacity on chest radiography. She then develops new hypotension (blood pressure 85/37 mm Hg, mean arterial pressure [MAP] 53 mm Hg) that is unresponsive to 2 L of lactated Ringer solution. After fluid resuscitation, the medical team inserts a pulmonary artery catheter (PAC), which reveals the following: central venous pressure (CVP) 13 mm Hg, pulmonary capillary wedge pressure (PCWP) 18 mm Hg, cardiac output (CO) 7.4 L/minute, cardiac index (CI) 3.7 L/minute/m², and MAP 58 mm Hg. Given these hemodynamic parameters, which one of the following shock states is this patient most likely experiencing?
- Vasodilatory
 - Obstructive
 - Hypovolemic
 - Cardiogenic
42. A 56-year-old man with a medical history of alcoholic cirrhosis complicated by ascites develops hypotension and new-onset confusion after his weekly paracentesis, requiring transfer to the medical ICU. On admission, the patient's Hgb is 5.9 g/dL. Pertinent vital signs and laboratory values are heart rate 135 beats/minute, blood pressure 88/46 mm Hg (MAP 60 mm Hg), temperature 99.7°F (37.6°C), respiratory rate 28 breaths/minute, WBC 8.2×10^3 cells/mm³, and lactate 5.4 mmol/L. The medical team places a central venous catheter (CVC), which reveals the following: CVP 2 mm Hg, $ScvO_2$ 55%, and Pao_2 96 mm Hg on 2 L nasal cannula. Which one of the following interventions is most appropriate to perform first for this patient?
- Increase F_{iO_2} .
 - Initiate dobutamine infusion.
 - Initiate piperacillin/tazobactam and vancomycin.
 - Give packed red blood cell (PBRC) transfusion.
43. A 58-year-old man with a medical history of non-Hodgkin lymphoma is currently on day 10 of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). His WBC is 0.1×10^3 cells/mm³. On the oncology floor, he develops worsened shortness of breath and hypotension unresponsive to fluid resuscitation, requiring transfer to the medical ICU and intubation. Pertinent vital signs include blood pressure 85/40 mm Hg (MAP 55 mm Hg), respiratory rate 40 breaths/minute, temperature 97.7°F (36.5°C), and pulse oximetry (Spo_2) 88% on F_{iO_2} 0.9. A CVC reveals CVP 15 mm Hg and $ScvO_2$ 51%. Transthoracic echocardiography (TTE) reveals a dilated RV with systolic dysfunction and small left ventricular (LV) cavity. Given these hemodynamic parameters, which one of the following shock states does this patient most likely have?
- Hypovolemic
 - Obstructive, impaired systolic contraction
 - Vasodilatory
 - Obstructive, impaired diastolic filling
44. A 68-year-old man with a medical history of hypertension and diabetes is admitted to the ICU with a chief concern of chest pain and shortness of breath. His 12-lead echocardiography reveals ST-segment depression in leads V2 and V3. On arrival, he was bradycardic (heart rate 55 beats/minute) and hypotensive (blood pressure 87/57 mm Hg, MAP 67 mm Hg). The medical team places a PAC, which reveals the following: CVP 16 mm Hg, PCWP 24 mm Hg, CO 3.2 L/minute, CI 1.8 L/minute/m², SVR 1400 dynes \times second \times cm⁻⁵, and Svo_2 50%. Which one of the following is the most likely cause of this patient's shock?
- Hypovolemic
 - Vasodilatory
 - Cardiogenic
 - Obstructive
45. A 39-year-old man with no known medical history is admitted to the medical ICU for H1N1 influenza complicated by acute respiratory distress syndrome (ARDS). He is treated with low tidal volume ventilation for ARDS. On day 5 of hospitalization, he develops a ventilator-associated pneumonia and subsequently goes into septic shock. Despite receiving 3 L of lactated Ringer solution, he remains hypotensive. He is initiated on norepinephrine. An arterial catheter is inserted with a pulse pressure waveform analysis device attached. Pertinent vital signs include heart rate 110 beats/minute in atrial fibrillation, and blood pressure 85/50 mm Hg (MAP 62 mm Hg) on norepinephrine 10 mcg/minute. The patient is breathing spontaneously over the ventilator with a respiratory rate of 20 breaths/minute (ventilator rate set at 14 breaths/minute). Which one of the following findings would best indicate the need for additional fluid administration in this patient?
- CVP 6 mm Hg
 - PPV 15%
 - CO/CI increase by 17% on the passive leg raising (PLR) test
 - Inferior vena cava (IVC) collapsibility 10%

46. An 84-year-old nursing home resident presents to the ED for treatment of urosepsis. Initial clinical values were heart rate 126 beats/minute, blood pressure 89/50 mm Hg (MAP 63 mm Hg), respiratory rate 27 breaths/minute, temperature 101.5°F (38.6°C), lactate 5.5 mmol/L, and WBC 14.5×10^3 cells/mm³. In the first 3 hours, he receives 4 L of 0.9% sodium chloride; blood cultures are obtained, and appropriate antibiotics are administered. Current pertinent clinical values are as follows: blood pressure 89/56 mm Hg (MAP 67 mm Hg) and urinary output 0.7 mL/kg/hour. Which one of the following is best to recommend for this patient?
- Repeat serum lactate.
 - Check procalcitonin.
 - Give 500 mL of 0.9% sodium chloride.
 - Initiate norepinephrine.
47. A 35-year-old woman (weight 87 kg) is admitted to the surgical ICU after an appendectomy complicated by appendiceal perforation and hypotension. In the operating room, the patient receives 5 L of lactated Ringer solution. Pertinent clinical values include heart rate 136 beats/minute, blood pressure 80/45 mm Hg (MAP 57 mm Hg), respiratory rate 12 breaths/minute without spontaneous breathing, temperature 101.8°F (38.8°C), lactate 5.6 mmol/L, and urinary output 0.1 mL/kg/hour. Bed-side echocardiography reveals IVC collapsibility of 15%. Which one of the following is best to recommend for this patient?
- Administer 1 L of 5% albumin.
 - Initiate norepinephrine.
 - Administer 1 L of 0.9% normal saline.
 - Initiate norepinephrine and give 1 L of lactated Ringer solution.
48. A 50-year-old woman with a medical history of interstitial lung disease on chronic steroids is admitted to the medical ICU after cardiac arrest caused by a respiratory arrest with return of spontaneous circulation after 2 minutes of cardiopulmonary resuscitation. On day 5 of hospitalization, she develops acute hypoxia and new-onset hypotension, which is unresponsive to 3 L of 0.9% sodium chloride. Pertinent clinical values include heart rate 129 beats/minute, blood pressure 83/50 mm Hg (MAP 61 mm Hg), respiratory rate 38 breaths/minute, temperature 100°F (37.8°C), lactate 4.7 mmol/L, and urinary output 0.3 mL/kg/hour. Which one of the following is best to recommend regarding initial vasopressor therapy for this patient?
- Norepinephrine
 - Epinephrine
 - Dopamine
 - Phenylephrine
49. A 68-year-old man with a recent history of pulmonary embolism (PE) on rivaroxaban presents to the ED after several episodes of hematemesis. Pertinent clinical values include heart rate 125 beats/minute, blood pressure 92/47 mm Hg (MAP 62 mm Hg), Hgb 5.2 g/dL, and lactate 5.1 mmol/L. A CVC reveals CVP 3 mm Hg and ScvO₂ 50%. Which one of the following most likely contributed to impaired oxygen delivery (Do₂) in this patient?
- Increased cardiac preload
 - Increased cardiac afterload
 - Inadequate hemoglobin
 - Elevated heart rate

Questions 50 and 51 pertain to the following case.

H.T. is a 78-year-old man with a medical history of atrial fibrillation and uncontrolled hypertension. He is receiving warfarin for stroke prevention. H.T. is admitted to the medical ICU with complaints of shortness of breath, dizziness, and fatigue and a 3-day history of melena. On physical examination, his extremities are cold to the touch. Pertinent vital signs include heart rate 130 beats/minute and blood pressure 90/45 mm Hg (MAP 60 mm Hg). Pertinent laboratory values include Hgb 5.9 g/dL (baseline 12.3 g/dL) and INR 5.9. A CVC reveals H.T. has a CVP of 2 mm Hg.

50. Which one of the following is the best transfusion goal for H.T.?
- Transfuse if hemoglobin less than 7 g/dL.
 - Transfuse if hemoglobin less than 7.5 g/dL.
 - Transfuse if hemoglobin less than 8 g/dL.
 - Transfuse if hemoglobin less than 9 g/dL.
51. H.T. is given 2 units of PRBCs, 2 units of fresh frozen plasma, and 3 L of 0.9% sodium chloride and initiated on a norepinephrine infusion. After these interventions, his heart rate is 120 beats/minute, blood pressure 88/55 mm Hg (MAP 66 mm Hg) on norepinephrine 15 mcg/minute, CVP 4 mm Hg, and urinary output 0.2 mL/kg/hour. Current laboratory values include Na 149 mEq/L, K 5.2 mEq/L, Cl 115 mEq/L, BUN 34 g/dL, SCr 1.5 mg/dL (baseline 0.9 mg/dL), lactate 4.2 mmol/L, Hgb 7.2 g/dL, Hct 22%, and INR 2.1. Which one of the following is best to recommend for H.T.?
- 1 L of 0.9% sodium chloride
 - 1 L of lactated Ringer solution
 - No additional fluid
 - PBRC transfusion
52. A 51-year-old woman with a medical history of coronary artery disease (CAD), type 2 diabetes, and hypertension presents to the ED with a chief concern of chest pain and shortness of breath. A 12-lead echocardiography reveals ST-segment elevation in leads V1–4. Pertinent clinical values on arrival included heart rate 70 beats/minute,

blood pressure 95/52 mm Hg (MAP 62 mm Hg), respiratory rate 24 breaths/minute, temperature 99.1°F (37.3°C), and Hgb 7.4 g/dL. A CVC placed in the ED reveals the following: CVP 16 mm Hg and Scvo₂ 48%. Which one of the following is the most likely cause of decreased Do₂ and hypoperfusion in this patient?

- A. Inadequate hemoglobin
- B. Increased preload
- C. Increased afterload
- D. Decreased CO

Questions 53 and 54 pertain to the following case.

R.G. is a 69-year-old man with a medical history that includes heart failure with reduced ejection fraction with implantable cardioverter defibrillator, CAD, MI (8 years prior) with percutaneous coronary intervention to the left anterior descending artery, diabetes, hypertension, and hyperlipidemia. Echocardiography from 6 months prior reveals a left ventricular ejection fraction (LVEF) of about 15%. R.G. presents to the ED with 3 days of worsening shortness of breath, together with a 20-kg weight gain over the past week. He has altered mental status, and pertinent laboratory test results show elevated lactate (5.8 mmol/L) and transaminitis. Initial vital signs include heart rate 105 beats/minute, blood pressure 85/40 mm Hg (MAP 55 mm Hg), respiratory rate 35 breaths/minute, temperature 98.8°F (37.1°C), and Spo₂ 94% on 6 L nasal cannula.

53. R.G. is transferred to the cardiac ICU, where the team places a PAC for further monitoring. His heart rate is 107 beats/minute. With which one of the following hemodynamic parameters would it be most appropriate to recommend dobutamine for R.G.?
- A. PCWP 28 mm Hg, CI 2.4 L/minute/m², MAP 70 mm Hg
 - B. PCWP 28 mm Hg, CI 1.2 L/minute/m², MAP 65 mm Hg
 - C. PCWP 12 mm Hg, CI 1.2 L/minute/m², MAP 65 mm Hg
 - D. PCWP 12 mm Hg, CI 2.4 L/minute/m², MAP 70 mm Hg
54. R.G.'s medical team decides to initiate dobutamine, after which he develops worsening hypotension. His current hemodynamic and clinical parameters are as follows: heart rate 110 beats/minute, blood pressure 87/45 mm Hg (MAP 59 mm Hg), CVP 20 mm Hg, Svo₂ 60% on dobutamine 5 mcg/kg/minute, lactate 3.7 mmol/L, and urinary output 0.6 mL/kg/hour. The team asks for a recommendation for a vasopressor. Which one of the following is best to recommend for R.G. in cardiogenic shock?
- A. Dopamine
 - B. Phenylephrine
 - C. Norepinephrine
 - D. Vasopressin
55. A 62-year-old man with a medical history of multiple myeloma presents to the ED with new-onset shortness

of breath and hypotension. Chest CT scan reveals a large saddle PE. The patient is initiated on parenteral anticoagulation, given 3 L of lactated Ringer solution, initiated on norepinephrine, and transferred to the medical ICU. On arrival, he is intubated and mechanically ventilated, and a CVC is placed. Pertinent vital signs include heart rate 129 beats/minute, blood pressure 86/50 mm Hg (MAP 62 mm Hg) on norepinephrine 8 mcg/minute, respiratory rate 38 breaths/minute, temperature 98.6°F (37°C), Spo₂ 89% on Fio₂ 0.7, CVP 12 mm Hg, and Scvo₂ 52%. Which one of the following is best to recommend for management of this patient's PE?

- A. Give alteplase 100 mg infused over 2 hours.
 - B. Do a TTE.
 - C. Give 1 L of 0.9% sodium chloride.
 - D. Check a troponin T.
56. A 48-year-old truck driver (weight 100 kg) presents to the ED with worsening shortness of breath after a 4-day cross-country trip. Contrast-enhanced chest CT scan reveals a PE in a segmental branch of the right pulmonary artery and no evidence of RV dilation. Pertinent vital signs and laboratory values include heart rate 114 beats/minute, blood pressure 100/78 mm Hg (MAP 85 mm Hg), respiratory rate 25 breaths/minute, troponin T 0.03 ng/mL, brain natriuretic peptide 65 pg/mL, lactate 0.9 mmol/L, urinary output 0.8 mL/kg/hour, and Spo₂ 92% on 12 L of high-flow nasal cannula. The patient is initiated on intravenous heparin. Which one of the following is best to recommend regarding thrombolytic therapy in this patient?
- A. Alteplase 50 infusion over 2 hours
 - B. Alteplase 100-mg infusion over 2 hours
 - C. Tenecteplase 30-mg bolus
 - D. No thrombolytic therapy

Questions 57 and 58 pertain to the following case.

S.W. is a 23-year-old woman (weight 62 kg) with Hodgkin lymphoma who was recently treated with chemotherapy (current absolute neutrophil count 400 cells/mm³). She presents to the medical ICU with hypotension and is given 3 L of 0.9% sodium chloride. After fluid resuscitation, S.W.'s clinical values include blood pressure 74/50 mm Hg (MAP 58 mm Hg), heart rate 125 beats/minute, respiratory rate 24 breaths/minute without spontaneous breathing, temperature 102.9°F (39.4°C), CVP 14 mm Hg, Scvo₂ 76%, lactate 4.8 mmol/L, and urinary output 0.1 mL/kg/hour.

57. Which one of the following is best to recommend regarding initial empiric antibiotics for S.W.?
- A. Vancomycin and piperacillin/tazobactam
 - B. Vancomycin, piperacillin/tazobactam, and amikacin
 - C. Meropenem
 - D. Azithromycin and ceftriaxone

58. S.W.'s bedside echocardiography reveals IVC collapsibility of 10%. Which one of the following is the best to recommend for S.W.?
- A. Initiate norepinephrine.
 - B. Initiate phenylephrine.
 - C. Give 1 L of 0.9% sodium chloride and initiate norepinephrine.
 - D. Give 1 L of 0.9% sodium chloride.

Questions 59 and 60 pertain to the following case.

J.L. is a 46-year-old woman (weight 57 kg) with a medical history of Crohn's disease who presents to the surgical ICU after a colectomy, requiring total parenteral nutrition postoperatively. On postoperative day 5, she develops shock secondary to a *Candida albicans* catheter-related bloodstream infection. She is given an antifungal and 3 L of lactated Ringer solution and initiated on norepinephrine. J.L.'s pertinent current clinical values are as follows: heart rate 125 beats/minute, blood pressure 85/43 mm Hg (MAP 57 mm Hg) on 10 mcg/minute norepinephrine, respiratory rate 26 breaths/minute, temperature 101.7°F (38.7°C), CVP 10 mm Hg, and Scvo₂ 74%.

59. Which one of the following is the best to initiate for J.L.?
- A. Phenylephrine
 - B. Epinephrine
 - C. Vasopressin
 - D. 1 L of 0.9% sodium chloride
60. The next morning, J.L.'s norepinephrine requirements, which had been stable overnight, increase from 8 mcg/minute to 24 mcg/minute. A bedside TTE reveals LV hypokinesia. Pertinent clinical values include heart rate 110 beats/minute, blood pressure 80/47 mm Hg (MAP 58 mm Hg), respiratory rate 24 breaths/minute, temperature 101.8°F (38.2°C), CVP 12 mm Hg, Scvo₂ 48%, lactate 5.8 mmol/L, and urinary output 0.2 mL/kg/hour. Which one of the following is best to recommend for J.L.?
- A. Initiate phenylephrine.
 - B. Increase norepinephrine.
 - C. Give 1L 0.9% sodium chloride.
 - D. Initiate dobutamine and increase norepinephrine.

Learner Chapter Evaluation: Management of Circulatory Shock.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

38. The content of the chapter met my educational needs.
39. The content of the chapter satisfied my expectations.
40. The author presented the chapter content effectively.
41. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
42. The content of the chapter was objective and balanced.
43. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
44. The content of the chapter was useful to me.
45. The teaching and learning methods used in the chapter were effective.
46. The active learning methods used in the chapter were effective.
47. The learning assessment activities used in the chapter were effective.
48. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

49. Distinguish between the various shock syndromes according to a patient's clinical and hemodynamic parameters.
50. Construct an initial resuscitation pathway that includes quantitative resuscitation for patients with shock.
51. Devise a treatment strategy for a patient with hypovolemic shock.
52. Design an appropriate resuscitation and treatment strategy for a patient with cardiogenic shock.
53. Delineate the role and place in therapy of thrombolytics for pulmonary embolism.
54. Develop a treatment pathway for the care of patients with severe sepsis or septic shock that incorporates the Surviving Sepsis Campaign guideline recommendations and management bundle.
55. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
56. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 57–59 apply to the entire learning module.

57. How long did it take you to read the instructional materials in this module?
58. How long did it take you to read and answer the assessment questions in this module?
59. Please provide any additional comments you may have regarding this module:

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ACLS and Post-Cardiac Arrest Management

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LEARNING OBJECTIVES

1. Justify the pharmacist's role in advanced cardiac life support (ACLS).
2. Demonstrate an understanding of an automated external defibrillator and how it is used in the setting of cardiac arrest.
3. Distinguish between intravenous, intraosseous, and endotracheal access and drug administration by each route in the ACLS setting.
4. Design pharmacotherapy for the arrhythmias commonly encountered in cardiovascular emergencies including pulseless ventricular tachycardia (VT)/ventricular fibrillation, pulseless electrical activity, asystole, bradycardia, atrioventricular block (first, second, and third degree), paroxysmal supraventricular tachycardia, stable VT (with a pulse), and torsades de pointes.
5. Evaluate pharmacologic agents used in ACLS with respect to mechanism of action, appropriate dosing regimen, and treatment role.
6. Justify targeted temperature management in patients with cardiac arrest.
7. Evaluate the need for antiarrhythmic and/or vasopressor therapy in post-cardiac arrest patients including dosing, administration, and monitoring plans.

ABBREVIATIONS IN THIS CHAPTER

ACLS	Advanced cardiac life support
AED	Automated external defibrillator
AHA	American Heart Association
AV	Atrioventricular
BLS	Basic life support
CPR	Cardiopulmonary resuscitation
ECC	Emergency cardiovascular care
EMS	Emergency medical services
ET	Endotracheal
IHCA	In-hospital cardiac arrest
IO	Intraosseous
OHCA	Out-of-hospital cardiac arrest
PE	Pulmonary embolism
PEA	Pulseless electrical activity
PSVT	Paroxysmal supraventricular tachycardia
ROSC	Return of spontaneous circulation
TCP	Transcutaneous pacing

TdP	Torsades de pointes
TTM	Targeted temperature management
VF	Ventricular fibrillation
VT	Ventricular tachycardia

[*Table of other common abbreviations.*](#)

INTRODUCTION

Sudden cardiac arrest is the leading cause of death in adults older than 40. Most cardiac arrests occur out-of-hospital, and despite treatment by emergency medical services (EMS), the survival rate to hospital discharge is about 12%. In-hospital cardiac arrest (IHCA) survival rates are almost double those associated with out-of-hospital cardiac arrest (OHCA), with a survival rate to hospital discharge of about 25% (Mozaffarian 2016). Overall survival rates can be increased by bystander involvement with early initiation of high-quality cardiopulmonary resuscitation (CPR) and use of an automated external defibrillator (AED). When these interventions are implemented

quickly in OHCA, the survival rate can increase to as much as 50% (Rea 2006). Therefore, the potential to significantly affect survival provides the basis for the first links in the chain of survival for OHCA, including immediate recognition of sudden cardiac arrest, activation of EMS, early provision of CPR, and rapid defibrillation. Later links in this chain of survival include provision of effective advanced life support and implementation of post-cardiac arrest care (Kleinman 2015). The early recognition link is a reminder to quickly identify the need for help and to either call for help (i.e., EMS) or instruct someone else to do so. The early CPR link is a reminder to initiate CPR as soon as possible after recognizing cardiac arrest. In CPR, initiating chest compressions should take precedence over rescue breathing because compressions are critical for maintaining blood flow to vital organs. The rapid or early defibrillation link serves as a reminder of the importance of electrical shocks and that defibrillation should occur as quickly as possible to improve a patient's chances of survival.

BASIC LIFE SUPPORT AND ADVANCED CARDIAC LIFE SUPPORT OVERVIEW

Treatment of patients with cardiac arrest encompasses providing basic life support (BLS), advanced cardiac life support (ACLS), and post-resuscitation care. The primary focus of BLS is circulation, airway, and breathing (C-A-B) (Kleinman 2015). However, which of these elements to perform is guided by the experience, number, and skills of the bystander. An untrained lay rescuer should at least do compression-only CPR, which involves providing chest compressions at a depth of at least 2 inches (but less than 2.4 inches) at a rate of 100–120 per minute. A trained lay rescuer should provide

rescue breaths at a ratio of two rescue breaths to 30 chest compressions until EMS arrives. If more than one person is available, individuals should rotate performing chest compressions every 2 minutes (or after five cycles of 30 chest compressions to two rescue breaths) to avoid arm fatigue resulting in suboptimal chest compressions.

Advanced cardiac life support provides a systematic approach for timing and selection of management strategies in the setting of rhythm disturbances when there is no pulse, including ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA), or asystole. Details of the various cardiac rhythms and their management will be discussed in detail later. However, one basic ACLS concept important to emphasize is the difference between defibrillation and cardioversion. Defibrillation is only used in shockable rhythms such as pulseless VT and VF; defibrillation shocks are asynchronous. Cardioversion infers that the electrical shock is synchronized to the patient's ECG. Synchronized cardioversion is a form of defibrillation used in the presence of a tachyarrhythmia with a pulse such as atrial fibrillation, atrial flutter, supraventricular tachycardia, and stable VT. Synchronized cardioversion of regular narrow-complex tachycardias should be done using 50–100 J, whereas cardioversion of irregular narrow complexes should be done using 120–200 J monophasic or 200 J biphasic. The rationale for synchronization with these arrhythmias is to avoid the shock being delivered during the vulnerable period of the action potential, a phenomenon called R-on-T, which can lead to life-threatening VT or VF. Both cardioversion and defibrillation can be achieved using a manual defibrillator or an AED. These devices are widely available in the community and are very user-friendly to assist in an emergency. The AED will also provide voice directions to the user. Keep in mind that while the AED is being placed, CPR should be ongoing and not interrupted until the AED begins analyzing the rhythm. Steps to follow when using an AED are outlined in Box 1-1.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic Life Support
- Medication admixing

[*Table of common laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Heart Association. [Advanced Cardiac Life Support Guidelines](#). 2015.

Box 1-1. Steps to Using an AED

- Confirm that the patient is unconscious, is not breathing, and has no pulse.
- Turn on the AED and follow voice commands.
- Attach the electrode pads as indicated by the diagram on the AED.
- Discontinue chest compressions once the AED begins analyzing rhythm.
- Deliver shock, if indicated, by pressing shock button; immediately continue chest compressions.
- If the AED determines that a shock is not indicated, immediately continue chest compressions.

AED = automated external defibrillator.

TEAM APPROACH TO ACLS — ROLE OF THE PHARMACIST

Pharmacists are an integral part of hospital code teams. Results of several studies indicate that having a pharmacist as a member of the code team reduces hospital mortality and improves compliance with ACLS guidelines (Draper 2008; Bond 1999). Although the pharmacist's role can vary, the expectations, given their expertise in drug therapy, include evaluating laboratory values and managing any abnormalities, evaluating any potential drug-related causes for the cardiac arrest (H's and T's), anticipating need for and preparing medications during the code, assessing the type of intravenous access (peripheral vs. central) for medication administration, calculating doses, administering medications (according to state and institutional regulations), and documenting administration of medications and other interventions. An additional role of the pharmacist is in the post-cardiac arrest period when vasoactive agents, antibiotics, and other medications may need to be ordered and prepared. Ideally, pharmacists who participate on code teams should have some level of critical care or emergency medicine training and complete BLS and ACLS certifications through the American Heart Association (AHA). Although pharmacists are most often looked to for medication assistance, they can also assist with chest compressions and defibrillation, as needed.

ACCESS FOR MEDICATION ADMINISTRATION

Intravenous Access

Establishing access for medication administration in patients in cardiac arrest can be attempted once CPR is initiated and defibrillation is administered, if needed. According to the 2010 AHA guidelines for CPR and emergency cardiovascular care (ECC), intravenous access is preferred to the intraosseous (IO) and endotracheal (ET) routes (Neumar 2010); the role of intravenous access was not reviewed in the 2015 guidelines. Regardless of the route selected, all drugs for administration in the ACLS guidelines are listed to be administered by either the intravenous or the IO route. In addition, access for drug administration should be established without interrupting chest compressions, if possible.

Once the decision is made to obtain intravenous access, the patient will need to be evaluated to determine whether a peripheral or central line can be inserted. Inserting a peripheral line is undoubtedly faster and easier to do than establishing central line access. However, the advantage to having central line access in patients with cardiac arrest is that higher peak drug concentrations and faster onset of action can be obtained. In studies evaluating the

pharmacokinetic differences between central and peripheral intravenous drug administration during CPR, peak drug concentrations were about 2–4 times higher with central line administration than with peripheral administration (Talit 1985; Doan 1984). In addition, peak drug concentrations are achieved in a shorter time with central (15–30 seconds) than with peripheral (30–60 seconds) intravenous administration. In the 2010 AHA guidelines for CPR and ECC, a class IIb recommendation is given to considering placement of a central line through either the subclavian vein or the internal jugular vein unless there are contraindications (Neumar 2010). Inserting a central intravenous line is more complex than inserting a peripheral line and may require interruption of CPR to facilitate proper placement.

Peripheral line access can be obtained through the antecubital fossa veins or external jugular vein. To enhance the efficacy of medications administered peripherally, they should be given as an intravenous bolus, administered as close to the heart as possible, and followed with a 20-mL normal saline flush. This flush will help facilitate delivery of the medication from the extremity to the central circulation. Elevating the extremity during and after medication administration may also help deliver the agent to the central circulation by the effects of gravity.

IO Access

If intravenous access cannot quickly be established, the 2010 AHA guidelines for CPR and ECC recommend the IO route as an alternative (Neumar 2010); the role of IO access was not reviewed in the 2015 guidelines. The IO route allows for rapid access (i.e., within seconds) and can be used not only for administering medications, fluids, and blood products but also for obtaining blood for laboratory monitoring. The IO space refers to the spongy, cancellous bone of the epiphysis and the medullary cavity of the diaphysis. An extensive network of blood vessels is contained within the IO space, which connects to the central circulation by a series of longitudinal canals. Because of the abundance of blood vessels in this space, fluids or medications administered to this area will rapidly be transported to the central circulation. Unlike peripheral veins, the IO space is considered non-collapsible, especially under conditions of shock, trauma, or hypovolemia.

Several studies have shown that IO access can be obtained significantly faster than either central or peripheral intravenous access (Reades 2011; Leidel 2009). Intraosseous access can be obtained in a patient using a manual method, an impact-driven device, or a battery-powered device. With the manual method, a hollow steel needle is inserted into the bone that has a removable trocar to prevent bone fragments from clogging the needles during the insertion process. The needle is placed perpendicular to the entry site; the health care provider then applies pressure with a simultaneous

twisting motion until a significant decline in resistance from the bone is felt and the needle enters the marrow space. Brand names of these manual needles include Near Needle Holder, Cook, Jamshidi, and Sur-Fast.

The three impact-driven devices approved by the FDA are FAST1, BIG, and NIO. These devices drive the needle into the medullary space through operator force or a spring-loaded mechanism. The FAST1 device inserts the needle into the manubrium of the sternum, whereas the BIG and NIO devices drive the needle into the medullary space of the tibia or humerus. The EZ-IO is a battery-powered device that uses a power driver to drill the needle into the medullary space of the tibia or humerus with a rotary motion. Although most ED physicians have stated that they prefer to use the proximal tibial site for IO injections, the humeral head site is gaining popularity because of the higher fluid flow rates and lower levels of discomfort that can be achieved at this site (Paxton 2009).

The literature contains many small studies and case reports evaluating the IO administration of drugs used in the adult and pediatric ACLS treatment algorithms. Many of these studies document the safe use of drugs by the IO route or evaluate the pharmacokinetic and pharmacodynamic effect of drugs administered by the IO route in animal models. According to the available evidence, the onset of action and peak concentration of drugs administered by the IO route appear comparable with the central or peripheral intravenous route (Anson 2014). Currently, there is little evidence regarding the efficacy and safety of these drugs given by the IO route in the setting of cardiac arrest during CPR administration. Nevertheless, the 2010 AHA guidelines for CPR and ECC do not identify any resuscitation drugs that should not be administered by the IO route.

Medications administered by the IO route can be given at the same dose that would be administered intravenously. In addition, a variety of intravenous fluids can be administered by the IO route, including 5% dextrose in water, sodium chloride, lactated Ringer solution, and hetastarch. Blood transfusions have also been successful using the IO route. When administering medications or fluids by the IO route, 10 mL of normal saline should be infused rapidly through the site after initial access to maintain optimal flow rates through the site. Any subsequently administered fluids or infusions will need to be given with a pressure-infuser bag to continue to maintain optimal flow rates through the site.

When using IO blood for routine laboratory tests, it is recommended to discard the initial 2 mL of blood when obtaining blood from the IO site after initial line placement; this volume may contain a mixture of blood and bone marrow cells, which could adversely affect the accuracy of the laboratory results. One study evaluated the correlation between various laboratory tests done with peripheral vein and IO blood samples. In this analysis, a significant correlation occurred between these samples for Hgb, Hct, RBCs, glucose, BUN, Scr, Cl,

total protein, and albumin. For the CBC, the WBC appeared to be higher and the Plt lower in the IO samples than in the intravenous samples. For the chemistry panel, the sodium and calcium concentrations in the IO samples were within 5%–10% of those obtained in the intravenous samples and were considered clinically acceptable. Bicarbonate concentrations appeared to be lower and potassium concentrations appeared to be higher in the IO samples than in the intravenous samples; both of these concentrations obtained from the IO site were within 25% of those obtained in the intravenous samples and were considered different (Miller 2010). The IO site is also reliable for obtaining blood gas measurements and for typing and crossmatching for blood transfusions.

Serious complications related to IO access are rare, occurring in about 0.3% of all insertion attempts (Greenstein 2016). However, health care practitioners should keep in mind that fluid or medication extravasation, compartment syndrome, infection, and pain may occur in patients in whom IO access has been obtained. Up to 29% of the complications may be attributed to medication or fluid extravasation at the IO site (Greenstein 2016). Risk factors for extravasation at the IO site include incorrect needle placement, excessive needle movement after placement, several punctures in the same bone, and an inappropriate needle length. If the needle moves past the medullary space and into the cortical bone on the other side, any infused fluids or medications may cause swelling inside the patient's muscle compartments, leading to compartment syndrome. In addition, using a large volume or a fast infusion rate through the IO site may increase the risk of compartment syndrome. The swelling that results can subsequently affect arterial and venous blood flow. Because this particular complication could lead to limb loss and potentially death, it is essential to monitor the IO site often for patency and signs of extravasation. If medication extravasation occurs in the surrounding tissue, anecdotal reports recommend administering the antidote that would normally be given for an extravasation with an intravenous line (e.g., phentolamine) (Greenstein 2016). As with any access site, a risk of infection is associated with the IO route either at the point of entry or within the bone. Although rare (0.6% incidence), osteomyelitis is the most common infectious complication associated with IO access (Rosetti 1985). Risk factors for developing osteomyelitis in patients with IO access include prolonged use of the site, bacteremia, administration of hypertonic fluids, and administration of highly concentrated medications. To minimize the risk of osteomyelitis, it is recommended to remove the IO line within 24 hours of insertion. Pain commonly occurs during insertion of the IO line and during infusion of fluids or medications under pressure, especially in patients who are conscious. Administration of lidocaine into the IO site before the initiation of medications or fluids has been recommended to alleviate this pain if the patient is conscious (i.e., in the post-cardiac arrest management period). Although

the lidocaine dosage used for IO-associated pain may differ between institutions depending on their protocols, the EZ-IO manufacturer has recommended infusing 40 mg of 2% preservative-free lidocaine through the site over 2 minutes in adults; the lidocaine should dwell in the site for 1 minute, followed by a 5- to 10-mL normal saline flush. Another 20 mg of 2% preservative-free lidocaine should then be infused into the site over 1 minute. If further analgesia is required, additional lidocaine doses of 20 mg may be used on an as-needed basis; however, these doses should not be administered more often than every 45 minutes.

ET Access

Endotracheal administration of drugs results in variable drug delivery and pharmacologic outcomes; therefore, this route is not preferred in the cardiac arrest setting. However, the 2010 AHA guidelines for CPR and ECC state that the ET route can be used for administering certain resuscitation drugs if intravenous or IO access cannot be established (Neumar 2010); the role of ET access was also not reviewed in the 2015 guidelines. Unlike the intravenous and IO routes, only a limited number of drugs can be administered by the ET route, including Naloxone, Atropine, Vasopressin, Epinephrine, and Lidocaine (mnemonic NAVEL). Although most of the evidence regarding use of these resuscitation drugs by the ET route has been in animal models, some data in humans also show that the absorption of these medications appears to be reasonable (Raymondos 2000; Prengel 1991; Howard 1990). Although the efficacy and safety of administering amiodarone by the ET route has not been evaluated in humans, a study of rats showed that ET instillation of a single dose of this antiarrhythmic resulted in pulmonary fibrosis (Reinhart 1996). Therefore, amiodarone should not be administered by the ET route.

Although absorption of naloxone, atropine, vasopressin, epinephrine, and lidocaine is reasonable by the ET route, lower overall plasma concentrations result compared with intravenous administration (Quinton 1987; McDonald 1985). Consequently, higher doses of these drugs are needed when using the ET route. The most appropriate dose to achieve optimal outcomes is not known; however, the general rule of thumb is to use 2–2.5 times the intravenous dose for the ET route (e.g., the recommended epinephrine dose for intravenous administration is 1 mg; the ET dose of this medication should be 2–2.5 mg). However, several animal studies suggest that this dosing recommendation for ET epinephrine is too low and may actually lead to hypotension and reduced organ perfusion because β -receptor stimulation may predominate at lower plasma concentrations. In one study, an ET dose of epinephrine that was 10 times the recommended dose of intravenous epinephrine was needed to increase the blood pressure (Manisterski 2002). Medications administered by the ET route must be diluted in 5–10 mL of normal saline or water. For epinephrine and lidocaine specifically,

relatively small studies have suggested that the absorption of these drugs is improved when diluted in water (Naganobu 2000; Hahnel 1990).

CARDIAC RHYTHMS

Cardiac Arrest Rhythms

Pulseless VT/VF

Pulseless VT and VF are the most common arrhythmias encountered in OHCA. The myocardium cannot maintain adequate cardiac output during these arrhythmias. When these arrhythmias are present for more than a few minutes, the myocardium is depleted of oxygen and myocardial ATP, the main energy source for the heart. Cardiopulmonary resuscitation is needed to increase myocardial ATP so that an electrical shock may be successful in achieving return of spontaneous circulation (ROSC). Therefore, once a patient with pulseless VT/VF is identified, CPR should be initiated immediately by providing chest compressions with minimal interruptions and defibrillation as soon as possible. A summary of the sequence for the management of pulseless VT/VF is outlined in Figure 1-1. Defibrillation should occur before provision of CPR if the defibrillator is immediately available. Defibrillation should be undertaken with an energy level of 120–200 J (or the highest setting possible) biphasic or 360 J monophasic. Although either type of device can be used, defibrillators using biphasic waveforms are preferred to monophasic devices because of their higher success rates in terminating pulseless VT/VF. Chest compressions should resume immediately after defibrillation for 2 minutes before doing a rhythm or pulse check. During this time, intravenous or IO access should be attempted. After this 2-minute period of providing CPR, a rhythm check should be conducted to determine whether the rhythm is shockable (i.e., the patient remains in pulseless VT/VF). If shockable, defibrillation should be done and CPR immediately resumed.

If pulseless VT/VF persists despite these initial CPR and defibrillation attempts, pharmacologic therapy may be considered. Despite the lack of evidence showing a survival benefit with drug therapy, vasopressor and antiarrhythmic drug therapy continue to play a role in managing pulseless VT/VF. When initiating pharmacologic therapy for pulseless VT/VF that persists despite CPR and defibrillation, vasopressor therapy should be given before considering antiarrhythmic therapy. Epinephrine is the only vasopressor recommended in the pulseless VT/VF treatment algorithm. According to the 2015 AHA guidelines for CPR and ECC, when pulseless VT/VF persists despite CPR and defibrillation, it is reasonable to administer epinephrine 1 mg by intravenous or IO injection every 3–5 minutes while the patient remains in pulseless VT/VF (Link 2015). Epinephrine is beneficial in this setting primarily because of its α_1 -adrenergic stimulating effect, which results in an increase in coronary and cerebral perfusion

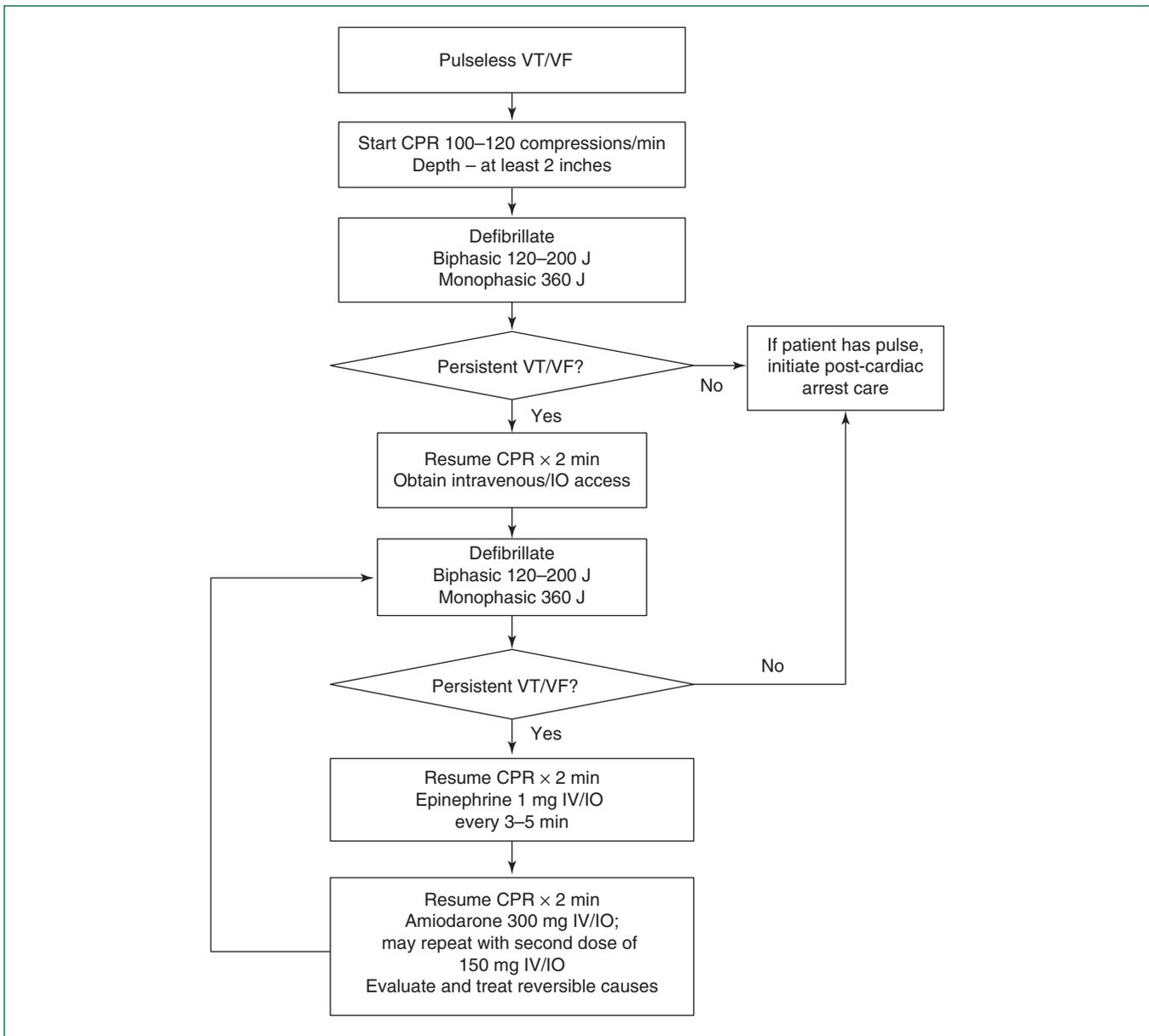


Figure 1-1. General treatment algorithm for pulseless VT/VF.

CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); IV = intravenous(ly); VF = ventricular fibrillation; VT = ventricular tachycardia.

Reprinted with permission from the 2015 American Heart Association Guidelines for CPR & ECC – Part 7: ACLS. ©2015 American Heart Association, Inc.

pressure. Vasopressin, previously recommended as an alternative vasopressor to epinephrine, has been removed from the pulseless VT/VF treatment algorithm in the 2015 AHA guidelines for CPR and ECC (Link 2015). This recommendation change is primarily based on the results of a prospective, controlled trial that enrolled 336 patients with OHCA (Mukoyama 2009). In this study, about 14% of the patients presented to the ED with PEA. The patients were randomized to receive a maximum of four doses of either vasopressin 40 units or epinephrine 1 mg on ED presentation. Patients who had received

doses of a vasopressor before presentation to the ED were excluded from the study. Overall, the treatment groups had no significant differences with respect to the rate of survival to hospital discharge or ROSC. In addition, the combination of vasopressin with epinephrine confers no significant benefit over epinephrine alone with respect to these end points in patients presenting with cardiac arrest (Ong 2012; Gueugniaud 2008).

Antiarrhythmic therapy should be considered in patients who remain in pulseless VT/VF despite the use of CPR,

defibrillation, and epinephrine. The 2015 AHA guidelines for CPR and ECC recommend amiodarone as the preferred antiarrhythmic; it may be administered by the intravenous or IO route (Link 2015). The initial dose is 300 mg and may be repeated at a dose of 150 mg if pulseless VT/VF persists after the third defibrillation attempt. Lidocaine may be considered as an alternative to amiodarone; the initial dose is 1–1.5 mg/kg by the intravenous or IO route and may be repeated at a dose of 0.5–0.75 mg/kg every 5–10 minutes if pulseless VT/VF persists (not to exceed a maximum total cumulative dose of 3 mg/kg). Neither amiodarone nor lidocaine has been associated with significantly improved survival with good neurologic recovery in this setting (Dorian 2002). The recommendation to use either antiarrhythmic agent is based on studies that have shown potential short-term benefit in outcomes.

An evaluation should always be done to identify any possible reversible causes for the cardiac arrest during the resuscitation process. A list of reversible causes that should be considered in patients with cardiac arrest is outlined in Box 1-2. A more detailed description of managing these reversible causes is discussed later in this chapter.

Pulseless Electrical Activity

Pulseless electrical activity, a form of sudden cardiac death, is defined as the presence of electrical activity in the absence of effective mechanical activity. Patients with this arrhythmia have no detectable pulse; however, some type of organized electrical activity (other than VT or VF) may be present on the ECG. Because of the misleading appearance of the ECG, it is essential to determine that the patient has no detectable pulse before initiating treatment. It is estimated that PEA accounts for 20% of all OHCA (Mader 2012). This rhythm disturbance may also account for almost 40% of first documented rhythms in patients with IHCA (Girotra 2012). Survival rates associated with PEA continue to be dismal, with less than 5% of patients with OHCA and about 10% of patients with IHCA caused by PEA surviving to hospital discharge (Myerburg 2013). Because of the significant mortality associated with PEA, practitioners must identify and treat any

potentially reversible etiologies of this rhythm disorder (see Box 1-2).

Pulseless electrical activity is considered non-shockable; therefore, high-quality CPR must be initiated immediately in patients with this rhythm disturbance. The 2015 AHA guidelines for CPR and ECC recommend that once CPR has been administered for 2 minutes in patients with PEA, a vasopressor should be administered (Link 2015). Epinephrine is the only vasopressor currently recommended for the treatment of PEA. The dose of epinephrine for PEA is 1 mg administered by the intravenous or IO route every 3–5 minutes throughout the cardiac arrest.

Vasopressin had previously been recommended for the treatment of PEA as a single dose to replace either the first or the second dose of epinephrine. However, as with pulseless VT/VF, vasopressin has been removed from the treatment algorithm for PEA in adults in the 2015 AHA guidelines for CPR and ECC (Link 2015). The PEA treatment algorithm is depicted in Figure 1-2.

Asystole

Asystole is a life-threatening heart rhythm characterized by an absence of electrical activity. It is often called *flat line* or *cardiac standstill* because of an absence of electrical activity. As a result, patients in asystole have no detectable pulse. Asystole is estimated to account for 45% and 35% of all OHCA and IHCA, respectively (Girotra 2012; Mader 2012). As with PEA, survival rates associated with asystole continue to be dismal and are similar to those previously reported for PEA.

Treatment of a patient in cardiac arrest as the result of asystole follows the same treatment algorithm as PEA (see Figure 1-2). Like PEA, asystole is considered a non-shockable rhythm; therefore, defibrillation is not recommended. Treatment of PEA includes high-quality CPR, epinephrine 1 mg by the intravenous or IO route every 3–5 minutes, and the identification and treatment of any reversible causes (see Box 1-2) (Link 2015).

Management of Potentially Reversible Causes of Cardiac Arrest

Hypovolemia

Hypovolemia is managed by early correction of the volume deficit. The choice of replacement fluid will ultimately depend on the type of fluid that is lost. In most cases, either normal saline or lactated Ringer solution should be used first and infused as rapidly as possible to restore tissue perfusion. Use of 5% dextrose in water should be avoided because of the risk of hyponatremia secondary to rapid reductions in serum sodium that may occur with its administration. Patients with hypovolemia secondary to blood loss should also receive blood products, and the source of the bleeding should be controlled. Fluid repletion should continue at a rapid rate until a desirable blood pressure is reached. Given the amount of volume that may be necessary to correct the patient's fluid deficit, electrolyte monitoring is also recommended, and any abnormalities should be managed accordingly.

Box 1-2. Reversible Causes of Cardiac Arrest

- Hypovolemia
- Hyperkalemia
- Hypokalemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypothermia
- Thrombosis – pulmonary
- Tension pneumothorax
- Tamponade – cardiac
- Toxins
- Thrombosis – coronary

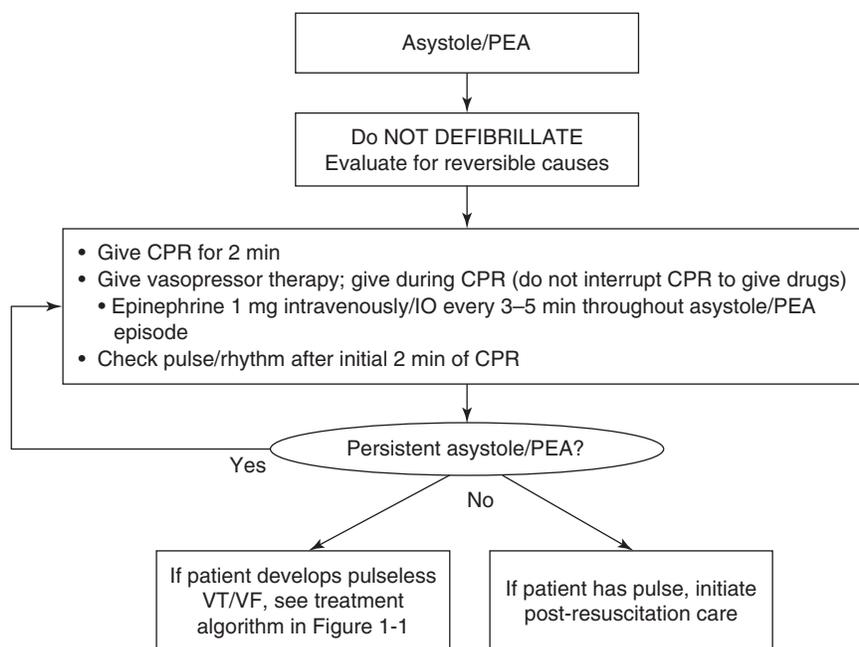


Figure 1-2. Treatment algorithm for asystole or pulseless electrical activity.

CPR = cardiopulmonary resuscitation; IO = interosseous(ly); PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

Information from: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132(suppl 2):S444-64.

Hyperkalemia

Hyperkalemia is a potentially lethal electrolyte disorder that can lead to cardiac arrhythmias and cardiac arrest. Hyperkalemia should be suspected in patients on dialysis who may have missed a dialysis session, who have acute kidney injury, or who are taking drugs that may lead to an increase in serum potassium concentrations (e.g., angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, aldosterone receptor antagonists, aliskiren, trimethoprim/sulfamethoxazole).

The treatment of hyperkalemia involves using drugs that inhibit the effect of potassium on the myocardium and decrease extracellular potassium concentrations. For patients with hyperkalemia in the setting of cardiac arrest, intravenous calcium chloride or calcium gluconate should be administered to stabilize the myocardium; these agents have no effect on serum potassium concentrations. The 2010 AHA guidelines for CPR and ECC recommend intravenous administration of 500–1000 mg (5–10 mL) of calcium chloride or 1.5–3 g (15–30 mL) of calcium gluconate over 2–5 minutes (Vanden Hoek 2010). In an emergency, it is usually more convenient to use calcium chloride because it is available as a 1-g prefilled syringe and is often stocked in code carts.

Therapies that can be used to shift extracellular potassium into the cells include insulin, sodium bicarbonate, and nebulized albuterol. The peak potassium-lowering effects of

insulin usually occur within 1 hour, with reductions of up to 1 mEq/L being possible. The 2010 AHA guidelines for CPR and ECC recommend intravenous administration of 10 units of regular insulin followed by 25 g (50 mL) of 50% dextrose (Vanden Hoek 2012). Although use of sodium bicarbonate for the treatment of hyperkalemia remains controversial, the 2015 AHA guidelines for CPR and ECC continue to recommend administration of this electrolyte. Most data regarding the potassium-lowering effects of sodium bicarbonate have involved the use of prolonged infusions, which have been associated with a reduction in serum potassium concentrations by 0.3–0.7 mEq/L. The recommended dose of sodium bicarbonate for hyperkalemia is 50 mEq administered intravenously over 5 minutes. However, sodium bicarbonate tends to be effective only in lowering serum potassium concentrations in patients with a non-gap metabolic acidosis. Nebulized albuterol can lower serum potassium concentrations by 0.6–1 mEq/L, with peak effects occurring within 90–120 minutes. The recommended albuterol dose is 10–20 mg nebulized over 15 minutes.

Once potassium has shifted into the intracellular space, efforts must be taken to remove excess potassium from the body. This act can be achieved using intravenous loop diuretics (e.g., furosemide), sodium polystyrene sulfonate, or dialysis. These treatment strategies can be initiated once a stable rhythm has been achieved.

Hypokalemia

Hypokalemia should be suspected in the setting of severe diarrhea, diuretic use, or malnutrition. Hypokalemia may cause prolongation of the QTc interval, which may lead to torsades de pointes (TdP). Treatment of hypokalemia involves potassium replacement by either the oral or the intravenous route. It is important to remember that, in general, for every 1-mEq/L decrease in serum potassium concentration, the potassium deficit is about 200–400 mEq. In mild to moderate hypokalemia (2.5–3.5 mEq/L), replacement with oral potassium is often sufficient. Although potassium can be replaced by the oral route in most hypokalemia cases, if the episode is severe (less than 2.5 mEq/L) and large potassium doses are needed, the oral route may be limited secondary to GI adverse effects; therefore, intravenous as well as oral replacement may be necessary in this situation. When replacing potassium by the intravenous route, the maximum rate of administration is 10 mEq/hour if given peripherally and 20 mEq/hour if given by central access. If the patient's only electrolyte abnormality is with potassium, potassium chloride can be used for repletion; in patients who have low serum potassium and phosphate concentrations, potassium phosphate can be used. A serum magnesium concentration should also be checked to ensure proper repletion of potassium. The concomitant presence of a magnesium deficiency can make it difficult to replete potassium stores solely using potassium (Huang 2007). Therefore, in patients with concomitant hypomagnesemia, it is important to replete the magnesium first and then proceed with potassium replacement.

Hypoxia

Hypoxia occurs secondary to a lack of oxygen delivery to the brain, heart, and other vital organs. In this setting, it is important to obtain airway patency and maintain respiratory effort. Treatment of hypoxia includes providing adequate oxygenation through proper ventilation and high-quality CPR.

Hydrogen Ion (Acidosis)

Acidosis occurs as a result of increased hydrogen ion concentrations in the blood and can be either metabolic or respiratory in nature. Acidosis occurs when the arterial pH falls below 7.35 (normal 7.35–7.45). Hydrogen ion acidosis (i.e., metabolic acidosis) can occur as the result of diabetic ketoacidosis, uremia, severe infection, or excessive ingestion of ethanol, salicylates (e.g., aspirin), and tricyclic antidepressants. Treatment of metabolic acidosis includes administering sodium bicarbonate as well as providing appropriate ventilation and high-quality CPR.

Hypothermia

Hypothermia is defined clinically as a temperature of less than 35°C (95°F). Patients who present with hypothermia may be rewarmed using passive external rewarming or active

internal rewarming. These processes may be accomplished using warming blankets, hot water bottles, or heat packs, as well as administering warmed intravenous fluids. Because defibrillation is often ineffective at low body temperatures, rewarming is crucial to successful resuscitation.

Thrombosis Pulmonary

Pulmonary embolism (PE) that progresses to cardiac arrest is associated with significant mortality. Although challenging, prompt diagnosis and subsequent treatment of this thromboembolic condition are critical. Use of thrombolytic therapy in patients with PE-induced cardiac arrest confers improved rates of ROSC and short-term survival (at 24 hours) (Böttiger 2001). Alteplase is the only thrombolytic agent currently FDA approved for the treatment of PE; the approved dosing regimen is 100 mg administered intravenously over 2 hours. However, in the midst of life-threatening PEA cardiac arrest, administration of a 2-hour infusion may not be completely practical. The 2015 AHA guidelines for CPR and ECC cite examples of thrombolytic regimens that can be administered in a more accelerated manner (Lavonas 2015). One example is alteplase 50 mg administered intravenously over 2 minutes followed by a second bolus dose if ROSC is not achieved within 30 minutes after the initial bolus dose. Another example is a single intravenous bolus dose of weight-based tenecteplase (30 mg for less than 60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; 50 mg for 90 kg or more). The accelerated dosing regimen of alteplase was associated with improved outcomes in patients with PE-induced cardiac arrest, and no significant benefit was associated with the tenecteplase regimen (Böttiger 2008; Böttiger 2001). According to the 2015 AHA guidelines for CPR and ECC, thrombolytic therapy is considered a reasonable treatment option for confirmed PE in the setting of cardiac arrest. In patients in whom PE is suspected, but not confirmed, this strategy may be considered.

Tension Pneumothorax

A tension pneumothorax occurs because of a progressive buildup of air in the pleural space. The cause is usually secondary to a laceration to the lung that then allows air to escape into the pleural space but does not allow air to move out. The buildup of air causes a shift in the mediastinum and ultimately leads to an obstruction of venous return to the heart that can cause cardiac arrest. Treatment of tension pneumothorax involves decompression by the insertion of a needle into the pleural space or placement of a chest tube.

Tamponade – Cardiac

Cardiac tamponade occurs when fluid or blood fills the pericardial space and restricts cardiac function. The amount of fluid in the pericardial space required to impair diastolic filling of the heart depends primarily on the rate at which the fluid accumulates in this space. If fluid or blood accumulates

rapidly in this space, as in trauma, tamponade can occur with as little as 100 mL of accumulation. In contrast, patients can often compensate for fluid or blood that accumulates in this space over a longer period because of the expansion of the pericardial sac; in these patients, 1000 mL of fluid or blood may accumulate without adversely affecting diastolic function of the heart. Treatment of cardiac tamponade involves pericardiocentesis or thoracotomy to remove the excess fluid or blood.

Toxins

Ingestion of toxins as well as overdoses of medications or street drugs are common causes of cardiac arrest. The biggest concern with drug overdoses is QTc prolongation that can result in TdP. For toxins, identifying the offending agent is needed so that an appropriate reversal agent (if available) can be administered. For example, naloxone can be administered to reverse the effects of an opioid and is now available OTC in many states for easier access.

Thrombosis – Coronary

A coronary thrombosis (or an ST-segment elevation myocardial infarction) occurs as the result of occlusion of a coronary artery with a thrombus. The occlusion cuts off blood supply to a portion of the heart and can lead to cardiac arrest, depending on the vessel occluded. Treatment includes either administration of fibrinolytic therapy or primary percutaneous coronary intervention, with the latter treatment being preferred. The fibrinolytics that may be administered include alteplase (weight greater than 67 kg: 15 mg intravenous bolus over 1–2 minutes followed by 50 mg over 30 minutes, then 35 mg over 1 hour; maximum dose 100 mg), tenecteplase (weight based, with a maximum dose of 50 mg for weight greater than 90 kg), and reteplase (10 units intravenously over 2 minutes, followed in 30 minutes by another dose of 10 units over 2 minutes).

Bradyarrhythmias

Bradycardia

Bradycardia is technically defined as a heart rate less than 60 beats/minute. However, patients who present with symptomatic bradycardia often have a heart rate less than 50 beats/minute.

Sinus bradycardia can be the result of either intrinsic or extrinsic causes. Intrinsic disease of the sinus node is commonly called “sick sinus syndrome.” A list of potential intrinsic and extrinsic causes of sinus bradycardia is outlined in Box 1-3. Sinus bradycardia is a relatively common finding in young, athletically active individuals and is often asymptomatic. The absence of symptoms despite bradycardia is likely because of a compensatory increase in stroke volume that will offset the reduction in heart rate, thereby leading

to no change in cardiac output. Patients who develop mild symptoms associated with sinus bradycardia may present with dizziness, fatigue, weakness, or even syncope. In severe cases of sinus bradycardia, patients may present with signs or symptoms of poor perfusion, including altered mental status, chest pain, hypotension, acute heart failure, or shock. Patients with sinus bradycardia who are either asymptomatic or mildly symptomatic do not require immediate treatment. If patients with sinus bradycardia develop signs or symptoms of poor perfusion, immediate treatment is warranted.

Initially, identifying and treating any potential underlying cause of sinus bradycardia is essential. The pharmacist should obtain a thorough medication history to determine whether the patient is taking any agents with negative chronotropic properties. The decision to continue these medications must consider their indication. For example, in patients with a history of heart failure with reduced ejection fraction or myocardial infarction, a permanent pacemaker may need to be implanted if a β -blocker is determined to be the cause of the bradycardia so that the patient can continue this mortality-reducing therapy. If the patient is taking a β -blocker solely for the treatment of hypertension, another, more preferred antihypertensive agent can be used. According to the 2010 AHA guidelines for CPR and ECC, first-line therapy for symptomatic bradycardia is atropine, a parasympatholytic drug that enhances both sinus nodal automaticity and atrioventricular (AV) nodal conduction through direct vagolytic action

Box 1-3. Intrinsic and Extrinsic Causes of Sinus Bradycardia

Intrinsic Causes

- Advanced age
- Myocardial infarction/ischemia
- Infiltrative diseases (e.g., sarcoidosis, amyloidosis, hemochromatosis)
- Collagen vascular diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
- Chagas disease
- Infective endocarditis
- Cardiac surgery (e.g., valve replacement, correction of congenital heart disease, heart transplantation)

Extrinsic Causes

- Drugs (e.g., β -blockers, verapamil, diltiazem, digoxin, ivabradine, clonidine, propafenone, amiodarone, dronedarone, sotalol)
- Electrolyte disturbances (e.g., hypokalemia, hyperkalemia)
- Hypoxemia
- Hypothermia
- Hypothyroidism
- Neurologic disorders associated with elevated intracranial pressure
- Neurocardiac syncope
- Carotid-sinus hypersensitivity
- Vasovagal reactions (i.e., coughing, defecation, urination, vomiting)

(Neumar 2010); the treatment of bradycardia was not reviewed in the 2015 guidelines. The recommended dose of atropine is 0.5 mg intravenously every 3–5 minutes. Doses less than 0.5 mg should not be used because they can paradoxically cause worsening bradycardia. A total maximum cumulative dose of 3 mg can be administered (i.e., six doses of 0.5 mg); administration of a total dose greater than 3 mg can result in complete vagal blockade. Atropine may induce tachycardia, which may result in poor outcomes in patients with myocardial ischemia/infarction. Therefore, atropine should be used cautiously in these patients. Of note, atropine is not effective for the treatment of bradycardia in patients who are undergoing targeted temperature management (TTM) or have undergone cardiac transplantation because vagal innervation is absent in the transplanted heart. Medications that have a more direct effect on the heart, including isoproterenol, aminophylline, and terbutaline, have been evaluated and shown to be modestly effective in the treatment of symptomatic bradycardia in cardiac transplantation recipients.

If atropine is not effective, either transcutaneous pacing (TCP) or a continuous infusion of a sympathomimetic

agent such as dopamine (2–10 mcg/kg/minute) or epinephrine (2–10 mcg/minute) should be initiated. Although isoproterenol is not officially included in the bradycardia treatment algorithm, the catecholamine is discussed as a second-line alternative in the 2010 AHA guidelines for CPR and ECC. Although isoproterenol is generally not regarded as a first-line agent in the treatment of bradycardia because of its adverse effects, this agent may be beneficial when bradycardia caused by an overdose of β -blockers is refractory to other therapies. Patients undergoing TCP can have significant pain and discomfort because of the higher energy levels required to stimulate the myocardium with this procedure. If TCP is being used in patients who are conscious, administration of a parenteral sedative (e.g., benzodiazepine) and/or analgesic (e.g., opioid) is recommended to enhance their level of comfort and ability to tolerate the procedure. If symptomatic bradycardia persists despite any of these measures, transvenous temporary pacing should be used. Patients having a diagnosis of sick sinus syndrome will likely require implantation of a permanent pacemaker. Figure 1-3 outlines a treatment algorithm for sinus bradycardia.

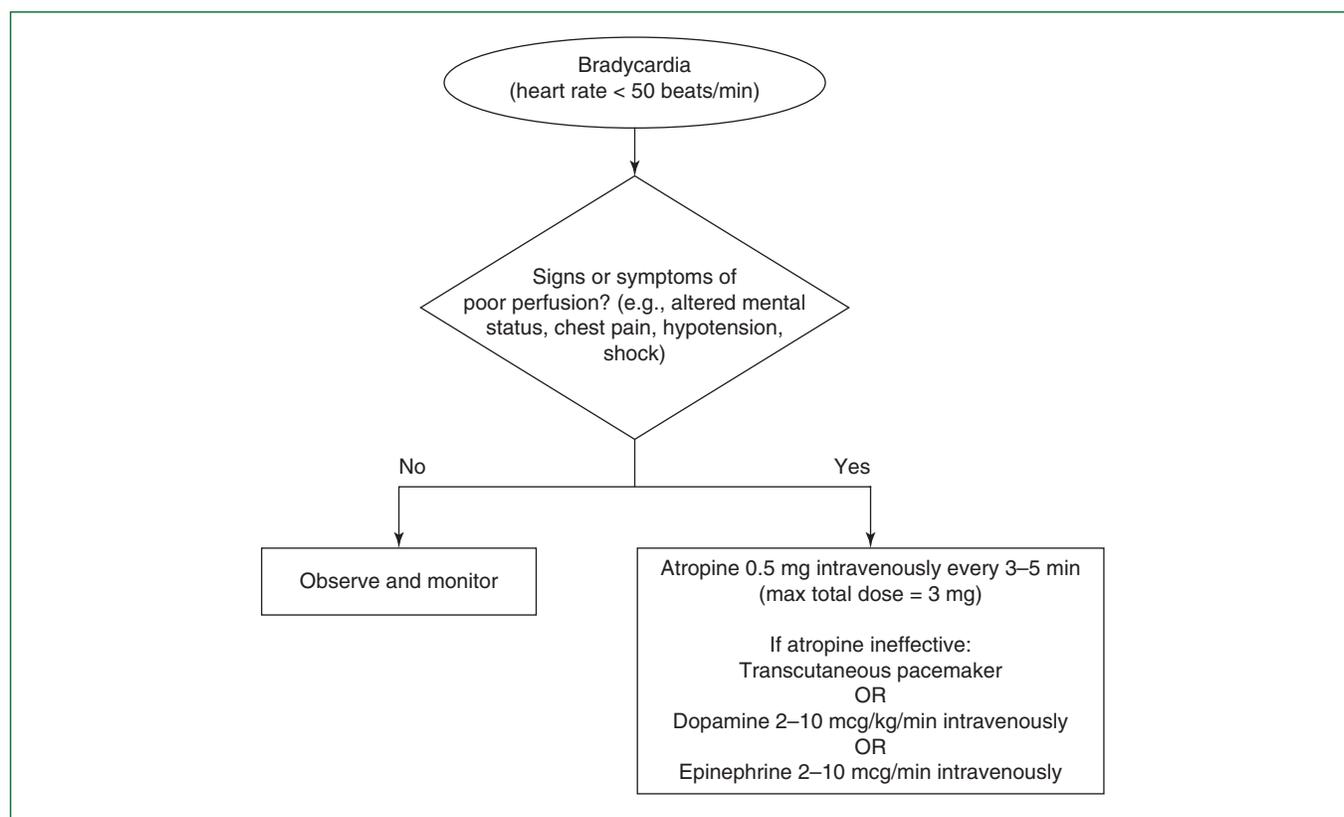


Figure 1-3. Treatment algorithm for bradycardia.

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AV Block

Atrioventricular block (i.e., heart block) occurs when atrial impulses emitted from the sinoatrial node are conducted either in a delayed manner or not at all to the ventricles; this block would occur when the AV conduction system is not refractory to conducted impulses. Three different types of AV block can be determined by the patient-specific ECG: first, second, and third degree. In first-degree AV block, the PR interval is prolonged (greater than 0.2 seconds), and there is 1:1 AV conduction with a P wave preceding each QRS complex; it usually represents delayed conduction in the AV node. Second-degree AV block is further categorized as either Mobitz type I or Mobitz type II. In Mobitz type I AV block, there is less than 1:1 AV conduction with progressive lengthening of the PR interval until a P wave fails to conduct; this form of AV block is also known as “Wenckebach block” and is usually the result of delayed conduction in the AV node. In Mobitz type II AV block, intermittently dropped ventricular beats occur in a random fashion without measurable prolongation of the PR interval between beats; this form of AV block is usually caused by conduction disease below the AV node in the His-Purkinje system. Third-degree AV block is also known as complete heart block and occurs when each P wave fails to conduct to the ventricles, resulting in complete AV dissociation (i.e., atria and ventricles are beating independently of each other). This form of AV block may be caused by disease at any level of the AV conduction system, including the AV node, His-Purkinje system, or bundle branches. The location of the block can be determined by evaluating the rate and the width of the QRS complex in the escape rhythm.

As with sinus bradycardia, the treatment of AV block should begin with identifying and treating any potential underlying causes. In the acute setting, treatment of patients with AV block is guided by whether they present with signs or symptoms of hypoperfusion. If the patient presents with signs or symptoms of poor perfusion, pharmacologic therapy is warranted, and the general treatment algorithm for bradycardia should be followed (see Figure 1-3). Atropine is unlikely to be effective in increasing the heart rate in patients with Mobitz type II or third-degree AV block because the location of the block is generally below the AV node. Atropine works by accelerating conduction through the AV node and not through any of the non-nodal tissues (e.g., His-Purkinje system, bundle branches). Consequently, patients with Mobitz type II or third-degree AV block should alternatively be treated with TCP or a β -adrenergic agonist (epinephrine or dopamine continuous infusion) while awaiting implementation of transvenous pacing. A specific scenario in which initial pharmacologic management may be bypassed occurs in patients with Mobitz type II or third-degree AV block when intravenous access cannot be obtained; in these patients, immediate TCP should be initiated. Transvenous pacing should be implemented in any patient who continues to be symptomatic despite the use of pharmacologic therapy and TCP.

Tachyarrhythmias

Supraventricular Tachycardia

Supraventricular tachycardia is an abnormal rhythm that occurs as a result of abnormal electrical activity within the heart. As the name implies, supra (meaning above the ventricle) originates at or above the AV node. The broad term *supraventricular tachycardia* encompasses several different rhythm disturbances, including atrial tachycardia, junctional tachycardia, AV nodal reentrant tachycardia, and AV reciprocating tachycardia. In the clinical environment, this rhythm disturbance is more commonly called paroxysmal supraventricular tachycardia (PSVT). Paroxysmal supraventricular tachycardia is caused by AV nodal reentry. This arrhythmia can develop rapidly and may resolve without intervention. Heart rates associated with PSVT vary but may be over 200 beats/minute. The rapid heart rate reduces cardiac filling time, which can lead to a reduction in blood pressure and cardiac output. This arrhythmia is most likely to occur in younger, relatively healthy individuals without underlying structural heart disease. Signs and symptoms common in patients presenting with PSVT include palpitations, dizziness, and chest pressure. Patients presenting with syncope are more likely to have a heart rate greater than 200 beats/minute.

In patients with PSVT who have mild to moderate symptoms, vagal maneuvers should be tried first. The more common vagal maneuvers include holding one's breath and bearing down (Valsalva maneuver), unilateral carotid massage (for patients younger than 65 and without carotid stenosis), coughing, and immersing the face in ice-cold water. If these maneuvers are ineffective and the patient continues to have intolerable symptoms, adenosine is considered the drug of choice. Adenosine is an AV nodal blocking agent that slows conduction through the AV node, thereby interrupting the reentrant pathway and subsequently restoring sinus rhythm. The standard dose is 6 mg administered rapidly by the intravenous route over 1–2 seconds, followed immediately by a 20-mL normal saline flush. The need for rapid administration is secondary to its short half-life (less than 10 seconds). If after 1–2 minutes the rhythm has not been terminated, a dose of 12 mg may be administered, which may be repeated a second time, if needed. A reduced adenosine dose of 3 mg is recommended for patients with a central line or heart transplant and in patients receiving carbamazepine or dipyridamole. Using the lower dose in these patients is recommended because administering 6 mg may lead to severe bradycardia, AV block, or even asystole. Higher drug concentrations and faster onset are achieved with central line administration compared with a peripheral line. Heart transplant recipients have an increased sensitivity to adenosine. Both carbamazepine and dipyridamole enhance the effects of adenosine and may increase the risk of developing severe AV block. Carbamazepine may inhibit the reuptake of adenosine, leading to increased adenosine concentrations,

whereas dipyridamole increases adenosine concentrations by inhibiting its reuptake and its deamination. Conversely, use of theophylline or large quantities of caffeine may result in a diminished effect with adenosine because both of these medications are adenosine receptor antagonists. However, no specific dosing recommendations for adenosine exist for patients currently taking theophylline or those who are significant caffeine consumers.

Adverse effects of adenosine include flushing (transient), chest pain, bradycardia, premature ventricular contractions, and possibly a very brief period of asystole. The initial rhythm was likely PSVT if adenosine administration successfully converts the rhythm. If adenosine administration does not terminate the arrhythmia, the rhythm is more likely to be atrial fibrillation, atrial flutter, or a junctional tachycardia. In this situation, longer-acting AV nodal blocking agents, such as β -blockers, or the non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) may be considered. In this particular situation, expert opinion should be obtained for more extensive evaluation of the rhythm. If at any time the patient becomes unstable (hypotensive, shortness of breath, altered mental status, chest pain, or signs of shock or acute heart failure), synchronized cardioversion is the treatment of choice.

Stable VT

Ventricular tachycardia is a regular, wide-QRS complex (greater than 0.12 seconds) tachycardia occurring at rates of 100–250 beats/minute. This rhythm disturbance is classified as either nonsustained or sustained. Nonsustained VT is defined as a run of VT of at least 3 beats terminating spontaneously in less than 30 seconds, whereas sustained VT continues for greater than 30 seconds. Ventricular tachycardia may also be either monomorphic or polymorphic. Monomorphic VT consists of QRS complexes that are similar in morphologic characteristics from beat to beat and is often caused by scar formation within the cardiac conduction system. Polymorphic VT consists of QRS complexes that vary in shape and/or size and is often associated with medications or myocardial ischemia. A classic form of polymorphic VT is TdP, which will be discussed later in this chapter.

In contrast to pulseless VT, stable VT is associated with a pulse. Initial management of stable VT should involve assessing circulation, airway, and breathing; initiating oxygen therapy if Sao_2 is less than 94%; obtaining an ECG to confirm the rhythm; and measuring the blood pressure. If a wide-complex tachycardia (i.e., VT) rhythm is confirmed, treatment options include intravenous amiodarone, procainamide, or sotalol. Intravenous amiodarone should be administered at a dose of 150 mg over 10 minutes to minimize hypotension. This dose can be repeated every 10 minutes for breakthrough VT, if needed. Once the VT is terminated, a continuous infusion of amiodarone can be initiated at a

rate of 1 mg/minute for 6 hours and then reduced to 0.5 mg/minute. To minimize the risk of hypotension, the total dose given over 24 hours should not exceed 2.2 g. If hypotension occurs with intravenous amiodarone, the infusion rate should be reduced; however, it is not necessary to discontinue the medication. The hypotension induced by amiodarone is secondary to the diluent, polysorbate 80, which has vasodilatory properties. Slowing the infusion rate should minimize this potential adverse effect. Alternatively, using the intravenous amiodarone formulation that is devoid of polysorbate 80 may be considered. Intravenous procainamide is administered as an infusion at 20–50 mg/minute until significant hypotension occurs, the QRS complex widens by more than 50% from baseline, a maximum dose of 17 mg/kg is reached, or the arrhythmia is suppressed. If the VT terminates with procainamide, a continuous infusion can be initiated at 1–4 mg/minute. Intravenous sotalol is administered at a dose of 100 mg (1.5 mg/kg) over 5 minutes. If one of these antiarrhythmic options fails to convert the VT to sinus rhythm, synchronized cardioversion should be considered.

Torsades de Pointes

A form of polymorphic VT, TdP is associated with delayed ventricular repolarization and manifests as prolongation of the QT interval on the ECG. Torsades de pointes (“twisting of the points”) is characterized by a twisting of the widened QRS complexes along the isoelectric line. The rate of TdP is typically 150–300 beats/minute. Medications that delay ventricular repolarization and cause QT interval prolongation are one of the main causes of TdP. Although TdP may be self-limiting and terminate spontaneously, it may also degenerate into VF and subsequent sudden cardiac death. If the causative agent is identified, it should be discontinued immediately. Patients with TdP (with or without a pulse) should undergo immediate defibrillation. Once a stable rhythm is restored (or even during defibrillation attempts), intravenous magnesium sulfate should be initiated to prevent recurrence of TdP. The recommended dose of intravenous magnesium sulfate for the treatment of TdP is 1–2 g, which can be administered by intravenous push or the IO route in the absence of a pulse or over 15 minutes in the presence of a pulse. A continuous infusion can then be administered at 2–4 mg/minute.

POST-CARDIAC ARREST CARE

Targeted Temperature Management

When cardiac arrest occurs, full-body ischemia ensues secondary to a lack of oxygen. In the brain, the lack of oxygen causes a loss of ATP production. In turn, this abnormality causes dysfunction of membrane ATP-dependent sodium-potassium pumps and results in glutamate release and subsequent nerve cell death. In addition to the significant ischemia that can occur during cardiac arrest, once

circulation is restored, reperfusion injury can result, which can result in a certain degree of nerve cell death. Three particular areas of the brain are most susceptible to injury as a result of prolonged ischemia: the cerebellar Purkinje cells, the cornu ammonis-1 area of the hippocampus, and the cerebral cortex. Significant injury to these areas will affect arousal and consciousness and may lead to a permanent vegetative or comatose state. Ultimately, many of the pathophysiologic processes in the brain that occur during cardiac arrest and ROSC are affected by temperature. As a result, therapeutic hypothermia may influence neurologic outcomes secondary to a potential neuroprotective effect. Although not all of the beneficial neurologic effects of therapeutic hypothermia are well understood, some of the proposed mechanisms involve reductions in glutamate release, neurotransmitter release, cerebral metabolism, free radical production, intracellular calcium, inflammation, and the rate of ATP depletion.

Literature Review

The concept of using hypothermia to alter neurologic injury began in the 1950s. The first study to evaluate this concept was conducted in dogs and showed reduced oxygen consumption in hypothermia. The initial study conducted in humans in 1959 showed a 50% survival rate in the hypothermia group (target temperature 31°C–32°C) compared with 14.3% in patients not cooled. Even though these benefits were shown many years ago, further research and subsequent adoption of hypothermia into clinical practice has evolved slowly. The pace of adoption accelerated significantly upon publication of two studies in 2002 that showed improved survival and neurologic outcomes in patients with OHCA secondary to pulseless VT or VF who were treated with hypothermia (Bernard 2002; Hypothermia After Cardiac Arrest Study Group 2002).

In the Hypothermia After Cardiac Arrest Study, 275 patients who had been successfully resuscitated from OHCA caused by pulseless VT/VF were randomized to either hypothermia (goal temperature 32°C–34°C) or normothermia. Exclusion criteria included patients who were in a comatose state before the cardiac arrest, pregnant, responsive to verbal commands after resuscitation, with a tympanic membrane temperature below 30°C, hypotensive (mean arterial pressure less than 60 mm Hg), hypoxemic (SaO₂ less than 85%) for more than 15 minutes after ROSC, coagulopathic, or terminally ill. The results showed a favorable neurologic outcome at 6 months in 55% of patients treated with hypothermia compared with 39% of patients in the normothermia group (p=0.009). In addition, 6-month mortality was 41% in the hypothermia group compared with 55% in the normothermia group (p=0.02) (Hypothermia After Cardiac Arrest Study Group 2002).

The other landmark study enrolled 77 patients who had successfully been resuscitated from OHCA secondary to VF but had remained in a persistent coma after ROSC. Patients were randomized to hypothermia (cooled to 33°C

or normothermia. Exclusion criteria included cardiogenic shock, women of childbearing age, or other causes of coma such as head trauma, stroke, or drug overdose. The rate of survival to hospital discharge with good neurologic outcome was significantly higher in the hypothermia group than in the normothermia group (49% vs. 26%, respectively; p=0.046) (Bernard 2002).

In contrast to the outcomes of using therapeutic hypothermia in patients with OHCA caused by pulseless VT/VF, studies that have evaluated the efficacy of therapeutic hypothermia in OHCA secondary to PEA or asystole have had conflicting outcomes. One study involving 125 patients who had nontraumatic OHCA resuscitated by paramedics were randomized to cooling using normal saline (at 4°C) or no cooling. Of these patients, 74 had non-VF arrest (34 from PEA, 39 from asystole, and 1 with unknown rhythm). Of the patients who made it to the hospital, there were no significant differences between the two treatment groups in the number of days to awakening, days to discharge, or days to death. However, there was a trend toward improved survival to discharge in patients who were cooled when the initial rhythm was VF. When breaking it down by rhythm, 69% of patients who had VF as their initial rhythm and underwent cooling awakened compared with 45% with an initial rhythm of VF who were not cooled (p=NS). In patients who presented with an initial rhythm other than VF, only 9% who underwent cooling awakened compared with 23% who were not cooled (p=NS). Unfortunately, this was a pilot study with a small sample size, thereby making it difficult to draw any definitive conclusions (Kim 2007). Other observational studies of OHCA with non-shockable rhythms found no significant difference in improved neurologic outcome on hospital discharge (Vaahersalo 2013; Dumas 2011).

In addition to the lack of clear data for the use of hypothermia in non-shockable rhythms, there is a lack of clarity with respect to target temperature and duration of hypothermia. One trial evaluated 950 unconscious adults after OHCA who were randomized to a controlled temperature of 33°C or 36°C; VF was the initial rhythm in 74% of the patients. The primary end point of all-cause mortality occurred in 50% of patients cooled to 33°C and in 48% of patients cooled to 36°C (p=NS) (Nielsen 2013). There are no comparative data evaluating the efficacy of various durations of hypothermia.

Candidates for Therapeutic Hypothermia

According to available information, the 2015 AHA guidelines for CPR and ECC recommend initiating therapeutic hypothermia in adult patients who are comatose in whom ROSC has been achieved after cardiac arrest (Callaway 2015). This recommendation is based on information from trials that showed few adverse effects from cooling and the high incidence of morbidity and mortality in the absence of any intervention. Even though the trials excluded many patients, the AHA has stated that therapeutic hypothermia is not contraindicated for any patient. Therefore, therapeutic hypothermia can be

initiated in patients with cardiac arrest caused by pulseless VT/VF or a non-shockable rhythm, regardless of whether the arrest occurs in or out of the hospital. Therapeutic hypothermia is considered a standard of care in all patients with cardiac arrest. However, for optimal benefit with good neurologic outcomes, cooling should be initiated as soon as possible after the insulting event.

The goal temperature for therapeutic hypothermia should be maintained at 32°C–36°C; however, in some circumstances, different temperature goals may be better. Specifically, patients who present with a lower body temperature (e.g., below 36°C) should be cooled to the lower temperature of 33°C rather than warmed to a higher temperature. Lower temperature goals may also be preferred in patients with clinical features that may be worsened at the higher temperature, as in cerebral edema or seizures. Higher temperature goals are preferred for those in whom a lower temperature may infer a higher risk (e.g., bleeding). Cooling should be maintained for at least 24 hours after achieving the goal temperature.

Cooling Process

Cooling may be accomplished by several different methods including ice packs, surface cooling, and endovascular cooling. Although infusion of cold saline was previously used in the prehospital setting, this method of cooling is no longer recommended. Ice packs should be placed on the groin, armpits, head, and both sides of the neck to maximize cooling, and cooling should be achieved at an average rate of 0.9°C/hour. Surface cooling involves the use of cold-water blankets, cold air-forced blankets, or cooling pads. The blankets are wrapped around the patient to facilitate cooling. The pads are hydrogel coated and are placed on the patient's thighs, abdomen, and back. The pads circulate temperature-controlled water under negative pressure and cool at a rate of 1.5°C/hour or faster. Endovascular cooling is an invasive cooling technique that requires circulation of blood through an extracorporeal circuit. Although the endovascular approach provides the most rapid cooling, its use is restricted to centers where extracorporeal devices are available and staff are trained to use these devices.

After the cooling period, patients must undergo a controlled rewarming process. The AHA offers no specific guidance on the rewarming process secondary to the lack of data; in general, patients are typically rewarmed at a rate of 0.3°C–0.5°C / hour until core body temperature is reached. Some patients may develop a fever after rewarming; because potentially worse outcomes may be associated with the presence of fever, active prevention should be undertaken in these patients.

Pharmacologic Therapy During TTM

As with any critically ill patient, pharmacologic therapy is often necessary during TTM to optimize patient care. The pharmacist must be acutely aware of the different aspects of TTM, the effect of TTM on medication pharmacokinetics and pharmacodynamics, and the medications that may be needed during the TTM process.

Shivering

Shivering is an anticipated reaction to hypothermia secondary to a reduction in core body temperature and is most likely to occur when body temperature drops below 36°C; however, shivering will diminish once the body reaches 34°C. Shivering is less than desirable because it increases heat production by 600%, leading to an increase in both core body temperature and oxygen consumption. Several pharmacologic agents may be used to help minimize shivering, including meperidine, serotonin receptor agonists, α_2 -adrenergic agonists, and neuromuscular blocking agents.

Meperidine works to negate shivering by acting on κ -opioid receptors and possibly through α_2 -adrenergic receptor-mediated actions. The usual meperidine dose for shivering management is 12.5–75 mg intravenously every hour as needed; use of higher meperidine doses can lead to added sedation and respiratory depression. In addition, in renal impairment, the metabolite of meperidine (i.e., normeperidine) can accumulate and increase seizure risk. Therefore, most single doses are limited to 25–50 mg, and adjunctive therapy with another agent is often used if the shivering is not controlled to minimize the adverse effects associated with meperidine.

Buspirone can also be used as adjunctive therapy to help reduce shivering. The mechanism by which buspirone reduces shivering is mediated centrally by serotonin receptors. Buspirone is not recommended as monotherapy because of its reduced efficacy when used alone; it is often used in conjunction with other agents such as meperidine to reduce the risk of adverse effects. In one small study, a dose of 30 mg of buspirone given in combination with meperidine worked synergistically to reduce the shivering threshold while causing minimal adverse effects, which included sedation and respiratory depression. In addition, the efficacy of the combination was similar to that with large meperidine doses used as monotherapy (Mokhtarani 2001). Buspirone doses used for hypothermia are 5–30 mg given orally every 8 hours.

Clonidine, an α_2 -adrenergic agonist, may also be used to help reduce shivering. Its effect in reducing the shivering threshold appears to occur in a dose-dependent fashion. Although the exact mechanism of how clonidine affects thermoregulation is not completely understood, it is thought to be mediated mainly through centrally distributed α_2 -adrenergic receptors. The clonidine doses evaluated for shivering are 3–9 mcg/kg orally and 0.15 mg intravenously. A randomized

trial compared the effect on shivering of a single dose of intravenous clonidine (0.15 mg) with that of a single dose of intravenous meperidine (25 mg). All 20 patients (100%) who received clonidine stopped shivering compared with 18 of 20 patients (90%) who received meperidine. The two patients in the meperidine group who continued to shiver after the initial dose ultimately received a second dose, which was effective. The average onset to a reduction in shivering was 2.7 minutes for meperidine and 3.1 minutes for clonidine (Schwarzkopf 2001). Therefore, either agent alone appears to be effective for controlling shivering. However, clonidine can cause bradycardia, which may further worsen the bradycardia that commonly occurs in the setting of therapeutic hypothermia.

Dexmedetomidine, a newer α_2 -adrenergic receptor agonist, is similar to clonidine but has an 8-fold greater affinity for the α_2 -adrenergic receptor. The dexmedetomidine dose for shivering is 0.2–0.7 mcg/kg/minute as an intravenous continuous infusion. Dexmedetomidine may not be optimal in TTM because it may worsen bradycardia and hypotension.

Neuromuscular blocking agents (e.g., cisatracurium, vecuronium) may also be administered during the cooling process. Typically, these agents are reserved for patients who continue to have signs of shivering despite the use of other therapies. The cisatracurium dose for shivering management is an intravenous bolus of 0.15 mg/kg, followed by a continuous intravenous infusion of 3 mcg/kg/minute that is titrated as needed according to response. Vecuronium is administered as an intravenous bolus of 0.08–0.1 mg/kg, followed by a continuous intravenous infusion of 0.8–1.7 mcg/kg/minute. Because vecuronium is renally eliminated, train-of-four monitoring is especially important in patients who likely have reduced renal perfusion because of the hypothermic state.

Sedation

All patients undergoing TTM should be sedated to minimize any pain or anxiety. Agents commonly used for sedation include the combination of fentanyl, midazolam, or propofol. Fentanyl may be administered at a dose of 50 mcg given by intravenous bolus every 2 hours as needed or as a continuous intravenous infusion initiated at 25 mcg/hour and titrated as needed. Midazolam can be administered at a dose of 2 mg given by intravenous bolus every 2 hours as needed or as a continuous intravenous infusion starting at 2 mg/hour and titrated as needed. Use of a benzodiazepine continuous intravenous infusion should be kept to a minimum to minimize delirium in the ICU. Propofol is initiated as a continuous intravenous infusion at a dose of 5 mcg/kg/minute and titrated every 5–10 minutes until adequate sedation is achieved. As with vecuronium, sedatives and analgesics that undergo hepatic and/or renal metabolism and elimination should be carefully monitored for accumulation during the hypothermic state because of reduced perfusion to these organs.

Other Adverse Effects Related to Hypothermia

In addition to shivering, pain, and anxiety, other adverse effects that may occur in TTM include bradycardia, electrolyte abnormalities, infection, renal impairment, coagulation issues, and respiratory issues. However, many of these adverse effects can easily be managed or even prevented using appropriate medications and monitoring.

From a cardiac and hemodynamic perspective, therapeutic hypothermia can result in a decrease in contractility and heart rate, with a resultant reduction in cardiac output by up to 25%. The bradycardia observed is thought to be secondary to a reduction in diastolic depolarization of the sinoatrial node. Electrocardiographic changes that may occur include increased PR and QT intervals, as well as widening of the QRS complex. An Osborn wave (i.e., a positive deflection occurring at the junction between the QRS complex and the ST segment) may also be revealed on the ECG; this wave is often characteristic of hypothermia when the body temperature falls below 32°C. Study data have shown that bradycardia in therapeutic hypothermia is associated with good neurologic outcomes in survivors of OHCA. In one study, 60% of patients with bradycardia had a more favorable outcome than 37% of patients without bradycardia ($p=0.03$). In fact, those with the lowest heart rates had significantly better outcomes than those with the highest heart rates ($p=0.027$) (Staer-Jensen 2014). Given these data, low heart rates should not be aggressively corrected in this setting. If treatment is needed (i.e., evidence of hemodynamic instability), atropine is unlikely to be effective, and other treatments such as isoproterenol, an increase in cooling temperature, or, if severe, transvenous pacing may be considered.

Electrolytes should also be carefully monitored in patients undergoing TTM because severe abnormalities, including hypomagnesemia and hypokalemia, can occur. These electrolyte abnormalities occur as a result of increased renal excretion and a subsequent intracellular shift. The role of magnesium in therapeutic hypothermia is multifold. Magnesium mitigates neurologic injury by reducing damage and cell death in the cerebral cortex and helping prevent brain damage secondary to reperfusion. Serum magnesium concentrations should be maintained at a normal to high-normal range. Potassium abnormalities such as hypokalemia often occur during the hypothermic phase, whereas hyperkalemia is more likely to occur during the rewarming phase. Hypothermia induces hypokalemia because of a transcellular shift of potassium into the intracellular compartment. This process is mediated by an increase in both sympathetic and β -adrenergic activity. On rewarming, potassium will then exit the cell, resulting in hyperkalemia. Therefore, careful consideration should be made regarding supplemental potassium during the hypothermic phase because over-supplementation can result in significant hyperkalemia during rewarming and may lead to arrhythmias that can be fatal.

Hypothermia can also increase the risk of bleeding. Increased bleeding times have occurred in patients secondary to impaired platelet function, reduced number of platelets, impaired production of clotting enzymes and tissue plasminogen activator inhibitor enzyme, as well as impairment of other steps in the clotting cascade. Platelets can be sequestered in the liver and spleen during hypothermia, but they may then reenter the circulation when the body is rewarmed. Other coagulation parameters such as PT and activated PTT (aPTT) will be prolonged if monitored at the cooled body temperature; PT and aPTT should be checked once the temperature falls below 37°C.

Patients should also be carefully monitored for the development of infection, hepatic impairment, renal impairment, arrhythmias, and hyperglycemia because these additional

complications can occur during the therapeutic hypothermia process. As previously suggested, reduced hepatic and renal perfusion may occur during hypothermia; therefore, monitoring for accumulation of sedatives, analgesics, and other drugs (e.g., antimicrobials) eliminated by these routes is imperative. If life-threatening arrhythmias occur during the hypothermic phase, cooling should be discontinued, and warming should be initiated. Hypothermia decreases insulin sensitivity and insulin secretion from the pancreas, which increase a patient's risk of developing hyperglycemia. Because high blood glucose concentrations are associated with increased morbidity and mortality, monitoring and control of blood glucose during hypothermia is necessary. Therefore, blood glucose concentrations should be maintained at 140–180 mg/dL during TTM.

Patient Care Scenario

J.S. is a 23-year-old man with no cardiac history who presents after a VF arrest while at work. Cardiopulmonary resuscitation was initiated immediately, and when EMS arrived, he was in VF and defibrillated × 1 with prompt ROSC. On arrival at the ED, he was agitated, diaphoretic, and unable to follow commands. Secondary to altered mental status and mixed metabolic and respiratory acidosis (serum lactate 10 mg/dL), J.S. was intubated. He received ketamine, etomidate, and succinylcholine for intubation, followed by a bolus of lorazepam and initiation of a propofol continuous infusion. His ECG and cardiac enzymes suggested no ST-segment elevation myocardial infarction or other cardiac abnormalities. He was not taking any medications before admission except for Adderall. His social history is significant for occasional cocaine use; however, his urine drug screen was negative. J.S. is transferred to the cardiac ICU, where

he can receive an advanced level of care and is initiated on TTM.

On arrival at the cardiac ICU, J.S.'s vital signs include temperature 37°C (98.6°F), blood pressure 120/63 mm Hg (mean arterial pressure 81 mm Hg), heart rate 114 beats/minute, respiratory rate 23 breaths/minute, Spo₂ avg: 99.2%, Min: 96%, Max: 100%

J.S.'s laboratory findings are as follows: Na 143 mEq/L, K 3.3 mEq/L, Cl 106 mEq/L, CO₂ 12 mEq/L, BUN 17 mg/dL, SCr 1.5 mg/dL, glucose 155 mg/dL, WBC 10.4 × 10³ cells/mm³, Hgb 15.1 g/dL, Hct 46.8%, Plt 334 10.4 × 10³ cells/mm³, total bilirubin 0.4 mg/dL, AST 69 IU/L, ALT 58 IU/L, ALK 57 IU/L, and albumin 4.4 g/dL.

Because J.S. is undergoing therapeutic hypothermia, what are appropriate recommendations for sedation, electrolyte replacement, blood pressure, antibiotics, and shivering management?

ANSWER

This patient should be continued on the propofol infusion and initiated on fentanyl, both titrated to a RASS (Richmond Agitation-Sedation Scale) score of -4. Because he is intubated and will not receive nutrition until rewarmed, he should receive stress ulcer prophylaxis as well. During the cooling phase, serum potassium concentrations can decline because of a transcellular shift of potassium into the intracellular compartment; therefore, his potassium should be replaced to a goal potassium of 4 mmol/L. A general guide is that 10 mEq/L of potassium replacement will increase serum potassium by 0.1 mEq/L. Once he completes the cooling phase, potassium should not be replaced because serum potassium concentrations can increase during this time secondary to potassium

exiting the cell, and significant hyperkalemia may result. Given his current MAP of 81 mm Hg (above the goal of 80 mm Hg), no additional vasoactive agent is needed to augment his blood pressure. Empiric antibiotics are not necessary during TTM unless the patient has active signs of infection, keeping in mind that fever will not serve as a reliable guide for detecting infection during the cooling phase. When this patient reaches the shivering threshold, he will likely need additional medications to manage his shivering. Therefore, meperidine 25–50 mg intravenously every 4 hours as needed should be ordered with buspirone 30 mg by nasogastric tube every 8 hours added if shivering is not controlled with meperidine alone.

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Blood Pressure Management

After cardiac arrest, patients may need blood pressure support. Many vasoactive agents may be used in this setting, with the choice of agent determined according to the patient's heart rate, systolic blood pressure, goal MAP, and risk of arrhythmia. In patients undergoing therapeutic hypothermia, a MAP above 80 mm Hg is preferred.

Dopamine

Dopamine is a metabolic precursor of norepinephrine that acts by stimulating α_1 , β_1 , β_2 , dopamine receptor D_1 , and dopamine receptor D_2 . Dopamine's mechanism of action is dose-dependent. At low doses (less than 2 mcg/kg/minute), dopamine acts primarily on dopamine receptors, leading to renal, mesenteric, and coronary vessel vasodilation; the primary effect at this dose is increased urinary output. At intermediate doses (5–10 mcg/kg/minute), dopamine acts primarily as a β_1 -agonist, resulting in increased heart rate and contractility. At high doses (greater than 10 mcg/kg/minute), dopamine primarily acts as an α_1 -agonist, leading to an increase in blood pressure through systemic arterial vasoconstriction. Dopamine is less potent than norepinephrine in vasopressor activity; however, it produces a greater increase in cardiac output than norepinephrine. In addition, the relationship between dopamine dose and receptor activity is patient-specific; therefore, a dopamine continuous infusion must be titrated to each patient's clinical response. Tachycardia may limit the ability to titrate dopamine. Dopamine may be used after ROSC for treatment of symptomatic bradycardia unresponsive to atropine or to augment blood pressure in the setting of significant hypotension.

Epinephrine

Epinephrine stimulates α_1 , α_2 , and β_1 -receptors, with less potent agonism at β_2 -receptors. The resulting physiologic effects of epinephrine are an increase in systemic vascular resistance, blood pressure, cardiac output, and heart rate.

After ROSC, epinephrine may be used for the management of symptomatic bradycardia unresponsive to atropine. Epinephrine may also be used for the management of hypotension. When making the decision to use either epinephrine or dopamine in this setting, the practitioner should be aware that epinephrine is more potent than dopamine and is more likely to cause organ ischemia.

For the management of symptomatic bradycardia, epinephrine is administered by a continuous intravenous infusion at 2–10 mcg/minute and titrated according to the patient's hemodynamic response. For the management of hypotension, epinephrine is administered by a continuous intravenous infusion at 0.1–0.5 mcg/kg/minute.

Of note, secondary to its potent β_1 activity, epinephrine is more arrhythmogenic than norepinephrine and phenylephrine. In addition, the risk of organ ischemia increases with the duration of epinephrine therapy because the vasoconstrictive

effects become more apparent with time. Epinephrine can cause hypoperfusion to any area of the body; however, regions most likely to be affected include the extremities, the GI tract, and the kidneys. Practitioners should routinely evaluate the color of the extremities; fingers or toes that are becoming hypoperfused will lose their pink color and become a dusky blue initially, which may then proceed to black if necrosis occurs. Renal function should also be routinely assessed because hypoperfusion to the kidneys manifests as increased BUN and SCr concentrations as well as a reduced urinary output. Hypoperfusion to intestinal organs can lead to gastritis, hepatic impairment, and/or intestinal ischemia. Monitoring the patient for abdominal pain, blood in the sputum or feces, decreased bowel sounds, and abnormal liver function tests is essential during prolonged epinephrine therapy.

Norepinephrine

Norepinephrine is a naturally occurring potent α_1 -agonist that also has β_1 -agonist activity, although with less potency. The physiologic effect of α_1 -induced vasoconstriction results in increased blood pressure, whereas the β_1 activity may result in increased cardiac output and heart rate. At lower doses, however, the effects on heart rate and cardiac output are minimal. Norepinephrine is indicated after ROSC for the management of severe hypotension. Norepinephrine may be preferred to dopamine and epinephrine because it has less effect on heart rate and is less arrhythmogenic. For the management of hypotension, norepinephrine is administered by a continuous intravenous infusion at 0.1–0.5 mcg/kg/minute and titrated according to the patient's clinical and hemodynamic response.

Phenylephrine

Phenylephrine is a pure α_1 -agonist with no activity at β -receptors; administration results in increased systemic vascular resistance and blood pressure, with no effect on heart rate. Phenylephrine is an alternative agent for maintaining blood pressure and organ perfusion after ROSC. Phenylephrine is administered as a continuous intravenous infusion at 100–180 mcg/minute and titrated according to the patient's clinical and hemodynamic response. Phenylephrine is optimal in patients at risk of tachycardia or arrhythmias because of its lack of effect on β -receptors.

CONCLUSION

Pharmacists play a significant role in caring for patients with both IHCA and OHCA. Clinical pharmacists can be of valuable assistance if a patient requires ACLS. Knowing how to do quality CPR, use an AED, and anticipate what medication and doses are needed during a cardiac arrest episode can help facilitate optimal ACLS management. The pharmacist's knowledge of drug distribution, metabolism, and elimination during therapeutic hypothermia can ensure appropriate medication selection and dosing.

Practice Points

When treating patients who have had either OHCA or IHCA, pharmacists should remember the following:

- Early provision of CPR and rapid defibrillation are important links in the chain of survival. These interventions have been associated with improved survival. Neither vasopressors nor antiarrhythmics have been associated with improved outcomes in this patient population.
- The primary focus of BLS is circulation, airway, and breathing. Remembering the acronym C-A-B will help you prioritize the steps to take once the patient has been identified as being in cardiac arrest.
- When considering medication administration during cardiac arrest, intravenous access is preferred to IO or ET access. Any of the medications recommended in the cardiac arrest algorithms can be administered by the IO route. Remember the acronym NAVEL when trying to recall the medications that can be administered by the ET route (naloxone, atropine, vasopressin, epinephrine, and lidocaine). Amiodarone should not be administered by the ET route because of the risk of pulmonary fibrosis.
- Epinephrine is currently the only vasopressor agent recommended for the treatment of pulseless VT/VF. Because of the lack of an observed benefit, vasopressin was removed from the treatment algorithm for pulseless VT/VF in the 2015 AHA guidelines for CPR and ECC. According to these guidelines, it is reasonable to administer epinephrine in patients who remain in pulseless VT/VF despite the provision of CPR and defibrillation.
- Antiarrhythmic therapy may be considered in patients with pulseless VT/VF who do not respond to CPR, defibrillation, and epinephrine. Amiodarone is preferred to lidocaine in this patient population.
- Both PEA and asystole are considered non-shockable rhythms. These cardiac arrest rhythms have the same treatment algorithm, which includes identifying any reversible causes, providing high-quality CPR, and administering epinephrine. Because of a lack of an observed benefit, vasopressin was removed from the treatment algorithm for PEA/asystole in the 2015 AHA guidelines for CPR and ECC.
- Remembering the H's and T's is helpful for recalling the list of potentially reversible causes of cardiac arrest. The H's include hypovolemia, hyperkalemia, hypokalemia, hypoxia, hydrogen ion (acidosis), and hypothermia. The T's include thrombosis (pulmonary), tension pneumothorax, tamponade (cardiac), toxins, and thrombosis (coronary).
- Atropine is the first-line therapy for symptomatic bradycardia. If the bradycardia persists despite the use of atropine, TCP or a continuous infusion of a sympathomimetic (dopamine or epinephrine) can be initiated. Transvenous pacing is considered last-line therapy if bradycardia persists despite these interventions.
- The goal MAP for patients undergoing TTM should be maintained above 80 mm Hg.
- Neuromuscular blockade should be reserved for use in patients in whom other treatment modalities for shivering management have failed.
- The goal temperature in patients undergoing TTM is 32°C–36°C, which is more liberal than in the previous guidelines, at 32°C–34°C.

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Self-Assessment Questions

1. A 75-year-old man presents to the ED with lightheadedness and fatigue. His medical history includes type 2 diabetes, hypertension, and gout. His current drugs include lisinopril 20 mg daily, metformin 1000 mg twice daily, and allopurinol 100 mg daily. All laboratory values are within normal limits. His vital signs are blood pressure 90/50 mm Hg and heart rate 36 beats/minute. A 12-lead ECG reveals sinus bradycardia. Which one of the following is the best initial treatment to recommend for this patient?
 - A. Adenosine 6 mg by intravenous push
 - B. Atropine 0.5 mg by intravenous push
 - C. Transvenous pacing
 - D. Vagal maneuvers

Questions 2 and 3 pertain to the following case.

T.S. is a 47-year-old man who presents to the ED with palpitations, stating that he “feels like his heart is racing.” He says that he has never had these symptoms before. His medical history includes a heart transplant secondary to ischemic cardiomyopathy (2006), coronary artery disease, hypertension, and general anxiety disorder. His current drugs include tacrolimus 2 mg twice daily, mycophenolate mofetil 500 mg twice daily, calcium carbonate 500 mg three times daily, lisinopril 20 mg daily, atorvastatin 10 mg daily, aspirin 81 mg daily, and amlodipine 10 mg daily. T.S.’s vital signs are blood pressure 110/67 mm Hg and heart rate 176 beats/minute. A 12-lead ECG reveals a narrow QRS complex tachycardia (regular). Given his ECG, T.S. receives a diagnosis of paroxysmal supraventricular tachycardia (PSVT).

2. Which one of the following, administered by intravenous push, would be the best initial treatment for T.S.’s arrhythmia?
 - A. Adenosine 3 mg
 - B. Digoxin 0.125 mg
 - C. Diltiazem 15 mg
 - D. Metoprolol 10 mg
3. The treatment given to T.S. fails to terminate the PSVT. Therefore, the decision is made to use electricity in an attempt to convert him back to sinus rhythm. His current vital signs are blood pressure 115/65 mm Hg and heart rate 170 beats/minute. His symptoms remain unchanged. Which one of the following is best to recommend for T.S.?
 - A. Defibrillation at 200 J monophasic
 - B. Synchronized cardioversion at 100 J biphasic
 - C. Defibrillation at 360 J monophasic
 - D. Synchronized cardioversion at 200 J biphasic

4. A 65-year-old woman is transported to the ED by emergency medical services (EMS) after having cardiac arrest with return of spontaneous circulation (ROSC). Her medical history includes type 2 diabetes, coronary artery disease, fibromyalgia, and hypertension. On ICU arrival, her vital signs are blood pressure 72/50 mm Hg and heart rate 115 beats/minute. She is undergoing targeted temperature management (TTM). The decision is made to initiate intravenous fluids and vasopressor therapy. Which one of the following access sites would be best to administer drugs through a central line to this patient?

- A. Antecubital fossa vein
- B. Deep brachial vein
- C. External jugular vein
- D. Internal jugular vein

5. A 55-year-old man presents to the hospital with acute decompensated heart failure. His medical history includes type 2 diabetes, coronary artery disease, and gout. His left ventricular ejection fraction is 15%. His current drugs include dobutamine intravenous infusion 5 mcg/kg/minute, aspirin 81 mg daily, lisinopril 5 mg daily, sliding-scale insulin, atorvastatin 40 mg daily, and bumetanide 2 mg twice daily. On hospital day 2, the patient’s urinary output declines, and his SCr is now 3 mg/dL (1.2 mg/dL at baseline). While on rounds, the team is called to the room because the patient was sitting up in bed stating he did not feel well and subsequently became unconscious with no detectable pulse. A code is called, and chest compressions are begun immediately. An evaluation of telemetry reveals ventricular tachycardia (VT). Anesthesia is called; however, in the interim, one of the medical residents is providing rescue breathing. After 2 minutes, a 120-J biphasic shock is delivered with resumption of chest compressions. Which one of the following is the best intervention to initiate next in this patient?

- A. Amiodarone 150 mg by intravenous push
- B. Cardiopulmonary resuscitation (CPR) for an additional 2 minutes
- C. Epinephrine 1 mg by intravenous push
- D. Intubation

Questions 6 and 7 pertain to the following case.

C.S. is a 65-year-old man who collapsed while working out on a treadmill. His cardiac arrest was witnessed, and bystander CPR was initiated. An automated external defibrillator (AED) showed that he was in pulseless VT. He was shocked twice and then had ROSC. Emergency medical services transported

him to the hospital. Given that C.S. was not immediately awake after resuscitation, TTM was initiated.

6. Which one of the following is the best process for initiating TTM for C.S.?
 - A. Reduce core body temperature to 32°C–36°C and continue hypothermia for 12 hours once goal temperature is reached.
 - B. Reduce core body temperature to 32°C–34°C and continue hypothermia for 24 hours once goal temperature is reached.
 - C. Reduce core body temperature to 32°C–36°C and continue hypothermia for 24 hours once goal temperature is reached.
 - D. Reduce core body temperature to 32°C–34°C and continue hypothermia for 24 hours.
7. C.S.'s core body temperature reached 32°C within 6 hours of his arrest. His vital signs are blood pressure 95/54 mm Hg and heart rate 32 beats/minute. His current drugs include propofol intravenous infusion 30 mcg/kg/minute, fentanyl intravenous infusion 50 mcg/hour, dopamine intravenous infusion 10 mcg/kg/minute, dobutamine intravenous infusion 5 mcg/kg/minute, and famotidine 20 mg by nasogastric tube twice daily. His heart rate drops to 20–25 beats/minute, and systolic blood pressure is 80–85 mm Hg. Which one of the following interventions is best to recommend for C.S.?
 - A. Administer atropine 1 mg by intravenous push every 3–5 minutes.
 - B. Increase his temperature to 34°C.
 - C. Increase the rate of dobutamine intravenous infusion to 7.5 mcg/kg/minute.
 - D. Initiate rewarming.
8. Which one of the following adverse effects is most likely to occur during the rewarming phase of TTM?
 - A. Hyperglycemia
 - B. Hyperkalemia
 - C. Hypokalemia
 - D. Increased bleeding time

Questions 9 and 10 pertain to the following case.

J.W. is a 43-year-old man with an unknown medical history who was brought to the hospital after an out-of-hospital cardiac arrest (OHCA). By report, J.W. is an avid biker and was preparing to leave his home for a ride when he collapsed. A neighbor who witnessed the event initiated CPR and called 911. On arrival at the hospital by EMS, the patient was unresponsive, and a 12-lead ECG revealed polymorphic VT. J.W. was defibrillated and CPR resumed with eventual ROSC. He remains unresponsive. The ECG post-resuscitation showed ST-segment elevation, and J.W. was taken immediately to the cardiac catheterization laboratory, where he was found to have almost complete occlusion of his left anterior descending artery. He

received two drug-eluting stents, and because of his lack of responsiveness after ROSC, he underwent TTM. After the percutaneous coronary intervention, J.W. has had intermittent episodes of nonsustained VT. His current drugs include famotidine 20 mg twice daily, aspirin 81 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, propofol intravenous infusion 60 mcg/kg/minute, fentanyl intravenous infusion 150 mcg/hour, dextrose 5% in water/0.45% sodium chloride at 75 mL/hour intravenously, and amiodarone intravenous infusion 1 mg/minute. On induction of hypothermia, J.W. begins shivering. His current vital signs are blood pressure 120/60 mm Hg and heart rate 60 beats/minute. Pertinent laboratory values include SCr 0.8 mg/dL.

9. Which one of the following would be the best initial treatment to manage shivering in J.W.?
 - A. Buspirone 30 mg orally
 - B. Clonidine 0.1 mg orally
 - C. Dexmedetomidine intravenous infusion 0.2 mcg/kg/minute
 - D. Meperidine 25 mg by intravenous push
10. About 4 hours later, J.W. reaches his goal temperature of 33°C. His current vital signs are blood pressure 90/56 mm Hg and heart rate 62 beats/minute. Which one of the following would be best to initiate for J.W. at this time?
 - A. Dobutamine to maintain his mean arterial pressure (MAP) above 60 mm Hg
 - B. Norepinephrine to increase his MAP to greater than 80 mm Hg
 - C. Epinephrine to increase his MAP to greater than 70 mm Hg
 - D. Dopamine at 15 mcg/kg/minute to increase his MAP to greater than 65 mm Hg

Questions 11 and 12 pertain to the following case.

G.D., a 75-year-old woman, is brought to the ED by EMS. Her daughter, who lives with her, states that G.D. began having severe dizziness and became confused this morning after breakfast. She did not lose consciousness at any time while at home. The daughter called 911 because she was worried her mother could be having a stroke. G.D.'s medical history includes chronic obstructive pulmonary disease, hypertension, and dyslipidemia. Her current drugs include hydrochlorothiazide 25 mg daily, amlodipine 10 mg daily, clonidine 0.1 mg twice daily, atorvastatin 40 mg daily, tiotropium inhaler 2 inhalations daily, and aspirin 81 mg daily. G.D.'s vital signs in the ED are blood pressure 85/50 mm Hg and heart rate 40 beats/minute. Pertinent laboratory values include K 4.3 mEq/L and magnesium 1.8 mEq/L. A 12-lead ECG reveals Mobitz type I atrioventricular (AV) block.

11. Which one of the following drugs is most likely contributing to G.D.'s current rhythm disturbance?
 - A. Amlodipine

- B. Clonidine
- C. Hydrochlorothiazide
- D. Tiotropium

12. A dose of atropine 0.5 mg by intravenous push is administered to G.D. After this dose, her vital signs remain unchanged. Which one of the following is best to recommend for G.D.?
- A. Adenosine 6 mg by intravenous push in 3–5 minutes
 - B. Atropine 0.5 mg by intravenous push in 3–5 minutes
 - C. Dopamine intravenous infusion at 15 mcg/kg/minute
 - D. Transvenous pacing

Questions 13 and 14 pertain to the following case.

R.F. is a 78-year-old woman who is brought to the ED from a long-term care facility after the staff found her to be increasingly confused over the past 2 days. This morning, R.F. also developed chills and a fever. She has a history of type 2 diabetes, hypertension, and stage 3 chronic kidney disease. Her current drugs include furosemide 40 mg daily, glipizide extended release 10 mg daily, irbesartan 300 mg daily, and linagliptin 5 mg daily. The irbesartan dose was increased 2 weeks ago because of poor blood pressure control. While being assessed in the ED, R.F. has dizziness and suddenly loses consciousness. She has no detectable pulse. Cardiopulmonary resuscitation is immediately initiated. Telemetry reveals sinus bradycardia at a rate of 45 beats/minute.

13. Which one of the following interventions is best for R.F.?
- A. Atropine 0.5 mg by intravenous push
 - B. Defibrillation at 120 J biphasic
 - C. Epinephrine 1 mg by intravenous push
 - D. Vasopressin 40 units by intravenous push
14. R.F. continues to have no pulse and the code continues; her laboratory results return and show K 6.8 mEq/L, magnesium 2.1 mEq/L, and SCr 3.2 mg/dL (no baseline available). A 12-lead ECG reveals first-degree AV block, PR interval 280 milliseconds, and QT interval 420 milliseconds. Which one of the following is best to administer to R.F.?
- A. Calcium chloride 1 g intravenously over 2 minutes
 - B. Furosemide 80 mg by intravenous push
 - C. Regular insulin 10 units by intravenous push
 - D. Transcutaneous pacing (TCP)
15. A 45-year-old man was admitted to the hospital yesterday with an ST-segment elevation myocardial infarction, for which he received thrombolytic therapy with successful reperfusion. During morning rounds in the coronary care unit, the patient states that he is having some chest pressure and shortness of breath. He suddenly loses consciousness with no detectable pulse. The telemetry monitor reveals ventricular fibrillation (VF). A code is

called, and chest compressions with rescue breathing are begun immediately. After 2 minutes, a 200-J biphasic shock is delivered with resumption of chest compressions. After another 2 minutes, the patient continues to be without a pulse and in VF. Another 200-J biphasic shock is administered followed by CPR resumption. The medical resident in charge of the code asks for a 300-mg dose of intravenous amiodarone to be administered. As the clinical pharmacist participating in the code, which one of the following is best to recommend administering to this patient?

- A. Amiodarone 300 mg intravenous push
- B. Atropine 1 mg intravenous push
- C. Targeted TTM
- D. Epinephrine 1 mg intravenous push

16. An 82-year-old woman (height 65 inches, weight 70.3 kg) is admitted to the hospital after falling at home and fracturing several ribs and her right humerus. She has a medical history of osteoporosis, dementia, and hypertension. On hospital day 3, the patient begins having episodes of delirium, for which the medical resident orders haloperidol 1 mg intravenously every 6 hours as needed (required three doses that day). On hospital day 4, the patient states that she is having palpitations and feels very dizzy, even while sitting up in bed. A 12-lead ECG reveals intermittent runs of polymorphic VT with a QT interval of 510 milliseconds. As the nurse steps away to find the medical resident, the patient loses consciousness. A 120-J biphasic shock is delivered, and ROSC is achieved. The patient has sinus tachycardia with blood pressure 105/85 mm Hg and heart rate 105 beats/minute. Pertinent laboratory values include K 4.5 mEq/L, magnesium 1.8 mEq/L, and SCr 0.9 mg/dL. Which one of the following is best to initiate in this patient?
- A. Lidocaine 70 mg by intravenous push
 - B. Amiodarone intravenous continuous infusion at 1 mg/minute
 - C. Potassium chloride 40 mEq by intravenous infusion over 2 hours
 - D. Magnesium sulfate 1 g intravenously over 15 minutes
17. Which one of the following medication regimens would be best to administer by the specified routes to a patient (weight 80 kg) who is in some form of cardiac arrest?
- A. Lidocaine 80 mg by intraosseous (IO) administration
 - B. Amiodarone 300 mg by an endotracheal (ET) tube
 - C. Atropine 0.5 mg by an ET tube
 - D. Epinephrine 2.5 mg by IO administration
18. A 58-year-old man with a medical history of rheumatic heart disease presents to the ED with chills and fatigue over the past week. He denies chest pain, dyspnea, or changes in mental status. He states that he had dental

work a few weeks ago and did not take any antibiotics before the procedure. Physical examination reveals petechiae over his legs, (+) Janeway lesions, and (+) splinter hemorrhages under the nail beds of his fingers. He also has a significant murmur over the aortic valve region. Echocardiography reveals a moderate-size vegetation on his aortic valve. His vital signs are blood pressure 115/70 mm Hg, heart rate 49 beats/minute, and temperature 38.2°C (100.8°F). Pertinent laboratory values include WBC 11×10^3 cells/mm³ and SCr 0.8 mg/dL. A 12-lead ECG reveals sinus bradycardia, PR interval 180 milliseconds, and QT interval 420 milliseconds, with intermittently dropped QRS complexes. Which one of the following rhythms is this patient most likely to have?

- A. First-degree AV block
 - B. Mobitz type I AV block
 - C. Mobitz type II AV block
 - D. Third-degree AV block
19. Which one of the following roles of an advanced cardiac life support (ACLS) team member would be considered most valued for a pharmacist?
- A. Administering a 1-mg dose of epinephrine from a multidose vial
 - B. Recording the events of the code to ensure timely medication administration
 - C. Reading laboratory values from the patient's medical record
 - D. Determining the appropriate concentration of epinephrine for central line infusion
20. A 59-year-old man with a medical history of coronary artery disease, hypertension, chronic kidney disease (on hemodialysis), and type 2 diabetes is recovering from triple coronary artery bypass grafting surgery. On post-operative day 1, he tells the nurse that he is feeling dizzy. The nurse measures his blood pressure as 70/40 mm Hg. A 12-lead ECG reveals a wide-complex VT at a rate of 140 beats/minute. Which one of the following is best to initiate in this patient?
- A. Lidocaine
 - B. Amiodarone
 - C. Procainamide
 - D. Adenosine

Learner Chapter Evaluation: ACLS and Post-Cardiac Arrest Management.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Justify the pharmacist's role in advanced cardiac life support (ACLS).
13. Demonstrate an understanding of an automated external defibrillator and how it is used in the setting of cardiac arrest.
14. Distinguish between intravenous, intraosseous, and endotracheal access and drug administration by each route in the ACLS setting.
15. Design pharmacotherapy for the arrhythmias commonly encountered in cardiovascular emergencies including pulseless ventricular tachycardia (VT)/ventricular fibrillation, pulseless electrical activity, asystole, bradycardia, atrioventricular block (first, second, and third degree), paroxysmal supraventricular tachycardia, stable VT (with a pulse), and torsades de pointes.
16. Evaluate pharmacologic agents used in ACLS with respect to mechanism of action, appropriate dosing regimen, and treatment role.
17. Justify targeted temperature management in patients with cardiac arrest.

18. Evaluate the need for antiarrhythmic and/or vasopressor therapy in post-cardiac arrest patients including dosing, administration, and monitoring plans.
19. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
20. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:



Beyond Randomized Placebo Controlled Trials in Cardiology

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LEARNING OBJECTIVES

1. Judge the utility of evidence from non-randomized placebo controlled trial clinical study designs to answer clinical questions.
2. Evaluate the validity and applicability of active control superiority trial data to patient care.
3. Evaluate the validity and applicability of noninferiority trial data to patient care.
4. Distinguish between types of traditional observational study designs.
5. Evaluate the validity and applicability of evidence from traditional observational study designs to patient care.
6. Distinguish between types of novel observational study designs.
7. Evaluate the validity and applicability of evidence from novel observational study designs to patient care.

ABBREVIATIONS IN THIS CHAPTER

ARI	Absolute risk increase
ARR	Absolute risk reduction
HF	Heart failure
HR	Hazard ratio
IPTW	Inverse probability of treatment weighting
NI	Noninferiority
NNH	Number needed to harm
NNT	Number needed to treat
RPCT	Randomized, placebo-controlled trials
RR	Relative risk
RRI	Relative risk increase
RRR	Relative risk reduction

[*Table of other common abbreviations.*](#)

INTRODUCTION

Randomized, placebo-controlled trials (RPCT) are commonly used to study the effects of drugs in cardiology. However, many other study designs are available to answer clinical questions relevant to cardiology pharmacotherapy (Guyatt 2014; Fletcher 2014; Streiner 2009).

Value of RPCT

The RPCT are most effective in evaluating efficacy of new therapies compared with a placebo control in ideal study conditions. The RPCT are the gold standard for evaluating therapeutic effectiveness, given that randomization, when properly done, reduces selection bias by balancing known and unknown prognostic confounding variables. These trials generate results with the least biased estimate of the treatment effect when they are well-designed and correctly executed (Guyatt 2014; Sedgwick 2014b).

Despite their advantages, RPCT also have some disadvantages or limitations. Given that they are conducted in ideal trial settings and often have strict inclusion and exclusion criteria, generalizability or applicability to the real world setting, commonly referred to as external validity, may be limited. In addition, comparison to a placebo control is often not the best comparison. A placebo control should be avoided when a certain therapy is established as the standard of practice in clinical practice. Comparing a new drug with a placebo control rather than the established standard therapy

raises ethical issues about denying potentially effective treatments to patients. Furthermore, some clinical questions, such as those with a primary goal of examining safety of therapies also raise ethical issues and may prohibit use of the RPCT study design (Guyatt 2014; Fletcher 2014; Sedgwick 2010d, 2010f, 2011e).

Alternative Study Designs

The several alternative study designs to RPCT include randomized active-control superiority trials, noninferiority trials, and observational studies. The more common observational study designs are the traditional designs, including prospective and retrospective cohort studies; case-control studies; and nested case-control studies. Additional novel observational studies include propensity score methods studies, case-crossover studies, and instrumental variable analysis studies.

These alternative study designs have some advantages over RPCT. Active-control, superiority trials, and noninferiority

trials allow the novel intervention to be compared with a gold standard control. This comparison is beneficial when there is an established gold standard therapy in routine clinical practice. In this way, these two study designs are more applicable to real life practice because the novel intervention is being compared with an appropriate comparison group. Advantages to the observational study designs include increased generalizability or applicability to the real world setting and the ability to examine and identify potential harms in large population-based settings. Observational studies conducted with large, population-based samples allow for the identification of adverse effects and comparative effectiveness outside of the strictly controlled clinical trial setting. For instance, clinical trials are of limited duration, but observational studies can track patients for many years and identify adverse effects that have a long latency period. Similarly, clinical trials are of limited size, whereas large observational studies are able to detect rare adverse effects and comparative effectiveness in the real world setting (Guyatt 2014; Fletcher 2014; Sedgwick 2010f, 2011c, 2011d).

The limitations of these alternative study designs are covered in the following sections. For active-control superiority trials and noninferiority trials, a common key issue is that when a suitable control group is not chosen, the value of the trial is reduced. For all observational study designs, selection bias and confounding are the main important limitations. However, some types of observational study designs and analytical methods are better at minimizing confounding, and this will be examined in the following.

RANDOMIZED ACTIVE-CONTROL SUPERIORITY TRIALS

Description, Advantages and Disadvantages

Randomized active-control superiority trials are very similar in design to RPCT except that the control or comparison group is not a placebo. Active-control trials should retain the major study design aspects of randomized, controlled clinical trials that are essential components to minimize the risk of bias. These elements include randomization and concealment of the randomization process, blinding, intention-to-treat analysis, and completeness of outcome follow-up.(Guyatt 2014; Sedgwick 2014B; Fletcher 2014)

If the active-control chosen in this study design is truly one of the gold standards used in clinical practice, then this study design will provide valuable evidence for clinician decision-making by estimating the treatment effect of the novel therapy compared with the standard of care. When this study is designed to include the essential methodology of randomized controlled trials as noted above, the risk of bias will be minimized, strengthening the credibility of the trial results.

The main disadvantage of active-control designs is that if the chosen control is not a valid option in current clinical practice, or is in fact a substandard therapeutic option

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of placebo-controlled trial RCT study design
- Sources of bias in conducting clinical studies, including confounding
- How to interpret study results, including, event rates, NNT, NNH, confidence intervals and p-values
- Gold standard therapies for hypertension, atrial fibrillation

[*Table of common laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Mulla SM, Scott IA, Jackevicius CA, et al. [How to use a noninferiority trial: users' guides to the medical literature.](#) JAMA 2012;308:2605-11.
- Sedgwick P. [Study design.](#) BMJ 2009;339:b5263.
- Normand SL, Sykora K, Li P, et al. [Reader's guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding.](#) BMJ 2005;330:1021.
- Deb S, Austin PC, Tu JV, et al. [A review of propensity-score methods and their use in cardiovascular research.](#) Can J Cardiol 2016;32:259-65.
- Delaney JA, Suissa S. [The case-crossover study design in pharmacoepidemiology.](#) Stat Methods Med Res 2009;18:53-65.

in clinical practice, then the findings from this type of trial are not helpful for decision-making. Furthermore, if the new intervention is being compared with a substandard active control, erroneous conclusions may result, providing misleading conclusions. If the study design does not also include the essential methodology of randomized controlled trials as noted above, the trial results may be biased. As with all randomized clinical trials, generalizability will be limited to the population enrolled based on the inclusion/exclusion criteria, and to the choice of the outcomes evaluated.

Critical Appraisal

In critically appraising a randomized active-control superiority trial, all of the standard validity criteria for placebo-controlled superiority trials also apply. These criteria include checking for randomization and concealment of the randomization list; determining if randomization was successful by checking for balance of the baseline characteristics, typically in “Table 1” of the clinical trial publication; blinding of the patient, clinician and study personnel; examining if there were additional co-interventions or contamination during the trial; checking whether there was missing outcome data at the end of the trial; and ensuring that a true intention to treat analysis was done (meaning that all patients were analyzed in the groups to which they were randomized).

One additional critical appraisal criteria for an active-control superiority trial is to examine the active control that is chosen as the comparison. The active-control should ideally be a gold standard in practice that has a well-defined treatment effect compared with placebo. Furthermore, the active-control comparison should be administered at the dose, frequency, and duration that is known to be effective for the condition that is being examined in the trial (Guyatt 2014).

Cardiology Example of Randomized Active-Control Superiority Trials

Table 2-1 examines the ELITE II trial as an example of a randomized active-control superiority trial. The table provides information on the study objective, design, validity criteria using a risk of bias grid (low, slight/possible, high), and a summary of the key study findings.

Methodologic strengths of the ELITE II trial include randomization, blinding, ITT analysis, inconsequential degree of missing outcome data, and equal treatment of groups during the trial. Weaknesses include unclear concealment of the randomization list and poor choice of active control. Although the investigators chose what might be considered a suboptimal active control in captopril, they still failed to find superiority of losartan over captopril for the important clinical outcome of mortality in a heart failure population.

Value of Study Type in Clinical Practice

Randomized active-control superiority trials are important for finding new therapies that might be superior to existing

therapies. They are crucial in advancing our therapeutic knowledge to improve interventions that may be applied in clinical practice.

RANDOMIZED CONTROLLED NON-INFERIORITY TRIALS

The objective of randomized controlled superiority trials is to determine whether a novel treatment is superior to placebo or an active-control in improving one or more surrogate or clinical outcomes. Randomized, controlled, noninferiority trials differ from superiority trials in that they were originally developed to determine if the effectiveness of the novel treatment is sufficiently close to that of the standard treatment with which it is compared. Because a noninferiority trial is not seeking to demonstrate superiority, the novel treatment being evaluated may in fact result in lesser efficacy or benefits in important clinical outcomes when compared with a standard treatment. To trade off this potential loss of efficacy or benefit compared with the standard treatment, the novel therapy must have some type of decreased burden (e.g., cost, convenience, safety) for the patient. It may be potentially safer, more convenient, less costly, better tolerated, or have some other type of distinct benefit (Mulla 2012; Guyatt 2014).

Description, Advantages, and Disadvantages

Noninferiority trials should retain the study design aspects of clinical trials that are important to minimize bias including randomization and concealment, blinding, intention-to-treat analysis, and completeness of outcome follow-up. However, noninferiority trials have additional unique study design criteria that must be assessed distinctly from randomized, controlled, superiority trials (Sedgwick 2013e).

Superiority trials are conducted with a framework of conservatism. That is, they are designed to “stack the deck” against the experimental group so that if a difference is found, it is felt that the treatment effect is at least that large and possibly larger. Investigators have a strong incentive to conduct a rigorous study to maximize the chance of finding a difference. However, a conservative design in a noninferiority study increases the chance of a no difference result and is biased towards noninferiority. Therefore, it is important to think about the critical appraisal of noninferiority studies differently.

The comparison group in a noninferiority trial must be the gold standard treatment whose effect has been well established, preferably by multiple, randomized, controlled trials versus placebo. It is important to determine whether the standard treatment effect was maintained (i.e., the intervention in the control group was appropriately administered as the gold standard treatment, appropriate clinical outcomes were measured that are important for the condition of interest, and the patient population was one that represents the most suitable target population). If the population, gold standard

Table 2-1. Critical Appraisal of ELITE II Randomized, Active-Control Trial

Population	HF Class II-III (few class IV) with LVEF \leq 40%
Intervention/Exposure	Losartan 50 mg daily (44 mg/day achieved) + placebo captopril
Comparison	Captopril 50 mg three times daily (94% on optimal dose) + placebo losartan
Outcome	All-cause mortality (1.5 year median follow-up)
Study Type	Randomized active-control superiority trial

Validity Criteria	Description/Comment	Risk of Bias		
		Low	Slight/ Possible	High
Suitable Active Control	Enalapril would be more appropriate control because of most prior evidence of benefit in heart failure trials; captopril more prone to nonadherence because of three times daily dosing and adverse effects			x
Randomization/ Concealment	Randomized, concealment unclear		x	
Similar Baseline Characteristics	Similar per Table 2-1	x		
Blinding	Patients, clinicians and outcomes assessors blinded	x		
Equal Treatment	No obvious contamination or co-intervention	x		
Complete Outcome Data	Only 2 patients without outcome data; unlikely to influence results	x		
Intention to Treat	Used ITT analysis	x		

Type of Outcome	Outcome	Captopril Risk (n=1574)	Losartan Risk (n=1578)	Hazard Ratio (95% CI) p value	Relative Risk Difference	Absolute Risk Difference	NNT/ NNH
Efficacy	All-cause mortality (primary end point)	15.9%	17.7%	1.13 (0.95, 1.35) p=0.16	RRI: 13%	ARI: 1.8%	N/A
Safety	Cough	2.7%	0.3%	Not given p<0.001	RRR:800%	ARR: 2.4%	NNH: 41

Information from: Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-7.

treatment regimen, or outcomes are not chosen suitably in a noninferiority trial, these aspects of study design could minimize the treatment difference between groups and bias the result towards noninferiority. Furthermore, an intention-to-treat analysis biases towards noninferiority. Therefore, both an intention-to-treat analysis and a per-protocol analysis (which gives the best case scenario of treatment differences between groups) must be conducted.

Finally, a clinically suitable noninferiority margin must be chosen. The noninferiority margin is the amount of loss of benefit or loss of efficacy that is allowed with the novel treatment compared with the standard treatment. It is often expressed as a relative or absolute percentage allowable

increased risk in the efficacy end point, an outcome that should be a pertinent one for the condition under evaluation. It cannot be too large and contain clinically meaningful differences. Investigators can use prior literature, clinical judgment, or complex statistical methods to determine the noninferiority margin for their trial. Clinicians should examine the methods for a justification of the margin that the investigators used, and not accept the investigator's margin without critical evaluation. For example, often, the statistically derived noninferiority margins are too large and include a clinically meaningful loss of benefit with use of the novel therapy. Therefore, readers of noninferiority trials must often determine their own noninferiority margin that does

not contain a clinically meaningful difference. This determination is done based on clinical knowledge and sensibility about how much loss of efficacy is likely clinically acceptable (Mulla 2012; Guyatt 2014).

A key advantage of noninferiority trials includes being able to use an active-control comparison where placebo-controlled comparisons would be unethical. Furthermore, this design allows a balanced tradeoff between a decreased burden (e.g., cost, convenience, safety) with the novel treatment and what should be a minor loss of efficacy compared with the standard treatment. Because noninferiority trials are randomized controlled trials, if well-designed and well-conducted, they maintain the design elements that reduce the risk of bias in clinical trials.

The two key disadvantages of noninferiority trials are: (1) the use of a margin that is too large, allowing for clinically meaningful loss of benefit; and (2) the use of a substandard comparison group. Because both can lead to adoption of inferior therapies, a careful critical appraisal of the unique aspects of noninferiority trials is essential.

Critical Appraisal in Clinical Practice

Critical appraisal of a noninferiority trial involves a few steps in addition to the validity criteria previously noted in appraising active-control superiority trials. These additional criteria include determining if the standard treatment effect has been maintained; examining the noninferiority margin; and determining whether both intention-to-treat and per-protocol analyses have been performed.

To determine if the standard treatment effect has been maintained, one needs to examine the patient population included in the trial, the control treatment that was used for comparison, and the outcomes that were chosen and measured. The patient population should be at high enough risk to be able to potentially find a difference between the novel intervention and the active control comparison. An excessively low-risk population biases towards noninferiority. The active-control comparison should be chosen carefully (as noted in the active-control superiority trial) because one way to conclude noninferiority is to sub-optimally administer the comparison treatment. Finally, the outcome chosen for the trial should be a patient-important, clinical outcome (that is, an outcome that is considered valuable to the patient) that has been examined in prior clinical trials for the condition of interest.

The other validity criterion specific to noninferiority trials is the examination of the noninferiority margin. Noninferiority trials are not concerned if the novel treatment is better, as long as it is “not much worse”. The extent of “not much worse” that is clinically acceptable is the most suitable noninferiority margin. Many noninferiority trials determine the noninferiority margin based on complex statistical calculations that have no clinical relevance. Clinicians should examine whether the investigator’s noninferiority margin is suitable (small enough to exclude a clinically meaningful difference); if not,

they instead should determine their own noninferiority margin within which any loss of benefit or efficacy is considered clinically acceptable. For clinical outcomes desirable to avoid (e.g., occurrence of a stroke), this margin is then compared with the upper limit of the confidence interval around the treatment effect to determine if any unacceptable loss of efficacy has occurred. When using their own more stringent noninferiority margin, clinicians should note that the study may become underpowered because the original sample size was to examine a larger noninferiority margin which would have required a smaller sample size.

Figure 2-1 uses absolute risk differences in event rates to illustrate graphically the various conclusions that are possible using the confidence interval in relation to the noninferiority margin. If noninferiority has been reached, investigators may subsequently test for superiority. It is important to note that performing a noninferiority assessment after a failed superiority test should be avoided as it represents a biased statistical analysis. In Figure 2-1, we see the first point estimate and confidence interval are not only below the noninferiority margin, they are also below 0 (the point of the null effect or no difference for absolute risk difference); therefore, we can conclude superiority. Should the point estimate and confidence interval be completely above or greater than the noninferiority margin, representing an absolute increase, as in the third scenario in Figure 2-1, this would be a conclusion of inferiority or statistically significant harm (Mulla 2012; Guyatt 2014).

An intention-to-treat (or analyze as randomized) analysis approach yields the most unbiased yet also most conservative estimate of treatment effectiveness in a superiority trial. Because the intention-to-treat approach may result in an underestimate of the treatment effect, it can bias towards and cause a misleading conclusion of noninferiority. For this reason, per protocol analysis, which typically overestimates or magnifies the treatment effect, is also an essential approach that must be used in noninferiority trials. Clinicians should ascertain whether both intention-to-treat and per-protocol analyses have been conducted. Ideally, we would like to find that both analyses result in a similar estimate of treatment effect. If the per-protocol analysis suggests a much larger difference between treatments, then we would be concerned that the intention-to-treat analysis approach had indeed biased towards noninferiority, and we would be less likely to trust the results (Guyatt 2014; Sedgwick 2013c, 2013d).

Cardiology Example of Randomized Controlled Noninferiority Trial

The ROCKET-AF trial is examined as an example of a noninferiority, randomized, controlled trial (Table 2-2). A noninferiority design was chosen by the investigators because rivaroxaban would relieve the inconvenient burden of drug-drug interactions and frequent INR monitoring required with the traditional anticoagulant (warfarin), yet it was not expected to be superior to warfarin in efficacy for stroke reduction.

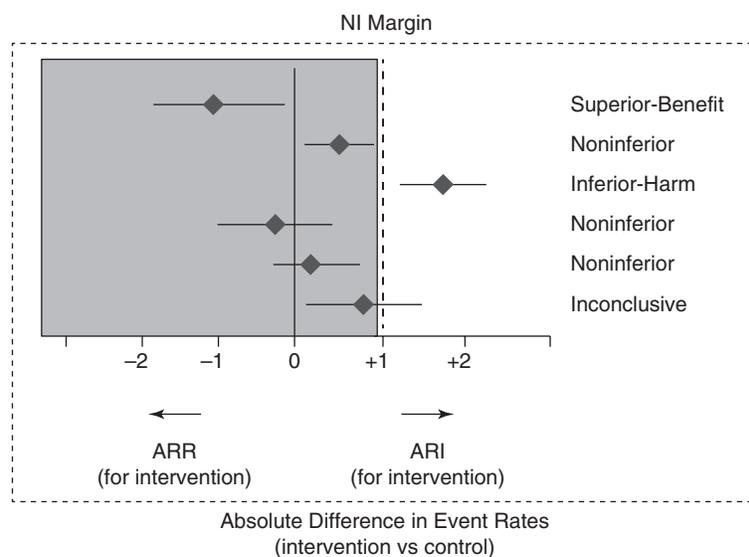


Figure 2-1. Using confidence intervals to examine for noninferiority. When the point estimate and confidence interval are below the noninferiority margin, noninferiority can be concluded. If the point estimate and confidence interval cross or include the noninferiority margin, the result is inconclusive or there is no difference in terms of noninferiority.

We can conclude that the ROCKET-AF trial has several study design features that put it at high risk of bias, making one less confident of the study results. Rivaroxaban was found to be non-inferior to sub-optimally managed warfarin with no difference in major bleeding episodes using the investigators noninferiority margin. Even if we consider a HR of 1.05 (a 5% relative increased risk of strokes with rivaroxaban), a potentially reasonable noninferiority margin for this condition and outcome, we would still conclude noninferiority. However, if our margin was HR of 1.05, and the upper confidence interval was 1.20, then the study results would be inconclusive or not noninferior. The number needed to treat is not calculated for noninferiority trials in which a conclusion of noninferiority is found, similar to not reporting number needed to treat when no difference is found in superiority trials.

Value of Study Type in Clinical Practice

Noninferiority trials are most valuable when a novel therapy has a meaningful reduction in some burden that the standard treatment possesses (e.g., less toxic, more convenient, less expensive) but it is not expected to be superior to the standard treatment. Noninferiority trials should be conducted only when superiority placebo-controlled or active-control randomized trials are not possible.

TRADITIONAL OBSERVATIONAL STUDY DESIGNS

In observational studies, the treatment or exposure of interest is not assigned, but participants are categorized based on natural or voluntary exposures or characteristics. In these

studies there is a good possibility that the exposed and unexposed groups differ in important ways other than the exposure of interest. This can lead to selection bias and confounding. Traditional observational study designs include prospective cohort studies, retrospective cohort studies, and case-control studies.

Data sources for traditional observational studies include longitudinal surveys, medical records, administrative databases, clinical data bases, and clinical registries. The use of population-based databases reduces sampling bias and improves generalizability.

Cohort Studies

Description, Advantages, and Disadvantages of Study Design

A cohort is defined as a common group of people. Cohort studies can be prospective or retrospective. In a comparative prospective, cohort study, a group of patients with some type of common characteristic is gathered, and patients are followed forward to determine who has had an exposure or characteristic of interest, and then followed forward to determine who developed the outcome of interest. In single group cohort studies, natural history of a disease can be ascertained. Retrospective cohort studies are similar to prospective cohort studies with the exception that defining the cohort exposure and outcome have all occurred in the past, whereas in a prospective cohort study, all of these occur in the future (Sedgwick 2010a, 2011b).

Overall, cohort studies are beneficial in that they can measure incidence, no treatment is withheld, they can examine

Table 2-2. Critical Appraisal of ROCKET-AF Non-Inferiority Trial

Population	Nonvalvular atrial fibrillation, median CHADS2 = 3.5
Intervention/Exposure	Rivaroxaban 15 or 20 mg daily depending on renal function
Comparison	Warfarin INR goal 2–3
Outcome	Stroke/systemic embolism (median follow-up 1.8 years)
Study Type	Noninferiority randomized controlled trial

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Maintained Standard Treatment Effect	The atrial fibrillation population was not too low risk; in fact, the CHADS2 score was higher than in other similar trials; warfarin is an appropriate gold standard comparison; however, time in therapeutic range was only 55%, much lower than optimal warfarin therapy and other novel oral anticoagulant trials (62%–68%); the outcome of stroke and systemic embolism was appropriate			x
Randomization/Concealment	Randomized and concealed randomization list	x		
Similar Baseline Characteristics	Mostly similar to Table 2-1; more patients with prior MI and CHADS2 of 6 in the warfarin group, biasing in favor of rivaroxaban		x	
Blinding	Patients, clinicians, and outcomes assessors blinded	x		
Equal Treatment	Low-dose ASA allowed in both groups; contamination possible—upon discontinuation of rivaroxaban in 23.7% of patients, they could be started on open label warfarin			x
Complete Outcome Data	3.3% of patients in both groups were missing outcome data; this may influence results because the percent of patients with missing data is larger than the percent absolute risk difference between groups			x
Intention to Treat and Per Protocol Analysis	Used ITT analysis and per-protocol analysis; results were larger with per protocol analysis, therefore, not consistent between both analyses		x	
Noninferiority Margin Suitable	Excessively large margin of HR=1.50 that includes a clinically meaningful increased risk of stroke			x

Type of Outcome	Outcome	Warfarin Risk (n=7133)	Rivaroxaban Risk (n=7131)	Hazard Ratio (95% CI) p value	Relative Risk Difference	Absolute Risk Difference	NNT/NNH
Efficacy	Stroke/systemic embolism (primary end point)	2.4%/yr	2.1%/yr	0.88 (0.75, 1.03) p<0.001 for NI	RRR: 12%	ARR: 0.3%	N/A
Safety	Major and non-major clinically relevant bleeding	20.3%	20.7%	1.03 (0.96–1.11) p=0.44	RRI: 3%	ARI: 0.4%	N/A

Information from: Patel MR, Mahaffey KW, Garg J, et al for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.

more than one outcome or exposure, and they can match or adjust for confounders. Advantages of prospective cohort studies include the ability to standardize exposure and outcome criteria at the start of the study, and the temporal sequence of exposure before outcome being insured by the prospective nature of the study. Advantages specific to retrospective cohort studies include that they are less expensive than prospective cohort studies, and it may be easier to acquire large sets of previously collected data in a retrospective manner using electronic health records and administrative databases.

Overall disadvantages of cohort studies are confounding, lack of blinding, and changing exposure over time. Prospective cohort studies may require many subjects and a long follow-up time, which may result in loss to follow-up and high operating costs. Disadvantages specific to retrospective cohort studies include possible recall bias (inaccuracy of recollections regarding past events). Also, when using data from medical records or administrative databases that are collected for non-research purposes, records may not contain all the desirable data in the format suitable to the researcher.

Critical Appraisal of Cohort Studies in Clinical Practice

Both prospective and retrospective cohort studies have similar major validity criteria for critical appraisal, including determining whether the study groups are balanced for baseline characteristics that are prognostic for the outcome of interest; whether the exposure occurred before the outcome; whether the exposure, and in particular, the outcome, is measured in a consistent way between groups; and whether there was complete and sufficiently long enough follow-up for the outcome of interest.

Observational studies will typically have unbalanced baseline characteristics because of lack of randomization to the study groups, which can result in confounding. For the unbalanced characteristics that might affect prognosis for the outcome, clinicians should examine whether the authors employed statistical methods to adjust for these baseline differences. Typical methods used for adjustment in traditional observational studies include stratification, matching, and multivariable regression. The investigators should have included all important potential confounders when using these adjustment methods. When examining the results, if a gradient of exposure (e.g., dose, duration, or recency of exposure) is also associated with a gradient of outcomes, this strengthens the observed association.

In addition to the criteria noted for examining prospective cohort studies, when examining retrospective cohort studies, one must pay special attention that the same data sources and methods were used for ascertaining the exposure and outcomes. There is a greater risk of surveillance bias (a type of information bias in which some patients are more closely

followed up than others, potentially leading to more outcomes being diagnosed in the closely monitored group) in retrospective studies, which primarily rely on data collected for administrative or routine clinical practice purposes (Normand 2005; Rochon 2005; Mamdani 2005, Sedgwick 2014c).

Cardiology Example of Cohort Study

A JAMA study on NSAIDs, bleeding and cardiovascular events in post-myocardial infarction patients by Olsen and colleagues is used as an example of a traditional retrospective cohort study (Table 2-3).

It is important to note that residual confounding is always a possibility with cohort studies. Although this study conducted an adjusted analysis, the methods of adjustment were not completely explicit and did not include some important factors known to be associated with increased bleeding risk (e.g., SSRI use). However, the adjusted hazard ratios are of moderate to high effect size, so even if there was some residual confounding, an increased risk of bleeding and cardiovascular events is still likely. Because of the large sample size, confidence intervals around the estimate are also precise.

Value of Study Type in Clinical Practice

One of the largest values of cohort studies is the ability to examine harm in the clinical practice setting or a population-based setting that cannot be done with randomized controlled trials. Often harms are less common and not possible to examine in a randomized trial because of a smaller sample size; harms appear after a longer onset and need a longer duration of follow-up; or the harms may only occur in the types of patients not included in the strict randomized controlled trial setting.

Case-Control and Nested Case-Control Studies

Description, Advantages, and Disadvantages of Study Design

A case-control study is a comparative study where people with the disease or outcome of interest (cases) are compared with a reference population that does not have the disease or outcome of interest (controls). This study begins with cases who have the disease of interest and the comparison group of controls without the disease. Both groups are investigated for previous exposures of interest. If previous exposure is more common among the cases, this is evidence that exposure is associated with the disease. This type of study design differs from other observational designs in that investigation begins with cases and works back to document possible causes of the illness. A nested case-control study incorporates the case-control approach, choosing both cases and controls from within an established cohort (Guyatt 2014; Fletcher 2014; Sedgwick 2010b, 2010c, 2010e, 2011a, 2013a, 2014a). Figure 2-2 is a schematic representation of the design of the case-control study.

Table 2-3. Critical Appraisal of NSAID, Bleeding and Cardiovascular Disease Events Cohort Study

Population	First-time myocardial infarction patients 30 years or older in Denmark, alive 30 days post-myocardial infarction using antithrombotics
Intervention/Exposure	NSAIDs
Comparison	No NSAIDs
Outcome	Bleeding requiring hospitalization and cardiovascular events (cardiovascular death, nonfatal recurrent MI and stroke)
Study Type	Retrospective cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Groups similar at baseline or statistical adjustment	The distribution of antithrombotic therapy was similar in NSAID and non-NSAID users at baseline; no comparison table of other baseline characteristics was provided to determine between group differences, making assessment for potential confounders difficult; the authors conducted an adjusted analysis, which included demographics, common comorbidities including previous bleeding and common cardiovascular drugs; the study did not adjust for some drugs, like SSRIs, that are known to be associated with bleeding risk		x	
Exposure precedes outcome	The exposure to NSAIDs was captured using time-varying covariates that allowed for changing NSAID exposures over time and only considered patients at risk when they were exposed to the specific NSAID; this was also done for the antithrombotic regimen, increasing accuracy of exposure categorization	x		
Outcomes measured similarly in groups	The Danish National Patient Registry, which includes all patients in the country, was used to measure outcome in both groups; outcomes were serious events unlikely to be influenced by surveillance bias	x		
Follow-up complete and long enough	Median follow-up of 3.5 years is a reasonable duration for outcomes of interest; a majority of recurrent CV events occur within the first year post-MI	x		
Dose-response gradient	There is a dose-response gradient such that the patient groups with a greater number of antiplatelet and anticoagulant drugs had higher risk of cardiovascular events and bleeding	x		

CV = cardiovascular; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

Information from: Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015;313:805-14.

Type of Outcome	Outcome	NSAIDs Risk (n=1931)	No NSAIDs Risk (n=60040)	Absolute Risk Difference	Unadjusted Relative Risk	Adjusted Hazard Ratio (95% CI) p value	NNH ^a
Safety	Bleeding requiring hospitalization	4.2%	2.2%	2.0%	RRI: 1.91	2.02 (1.81-2.26) p value not given	47
Safety	Major CV event	11.2%	8.3%	2.9%	RRI: 1.35	1.40 (1.30-1.49) p value not given	34

^aUsing adjusted hazard ratio obtained from [online converter](#).

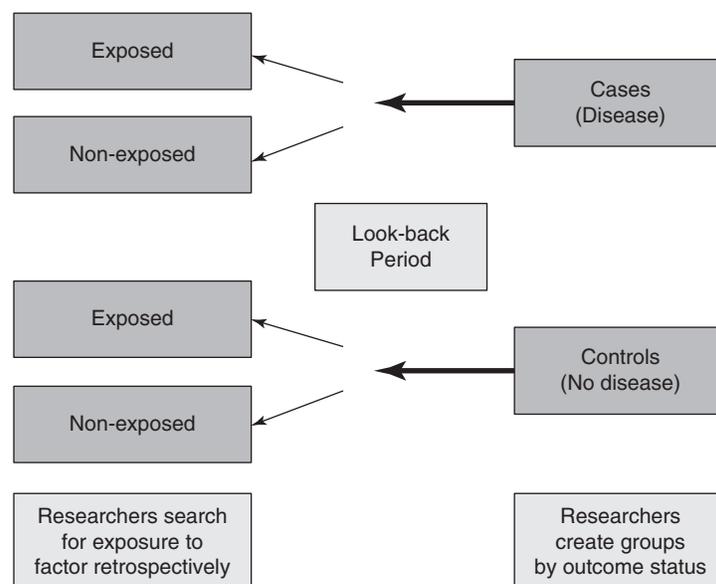


Figure 2-2. Case-control study design schematic.

Case-control studies are especially useful for uncommon or rare outcomes where it would take many years to obtain sufficient cases if a prospective study were conducted. Therefore, these studies can save time and money. If a nested case-control study takes the cases and controls from a population-based cohort, this method increases the study design validity.

Disadvantages of case-control studies include uncertainty of the temporal relationship between the exposure and the disease outcome because information on both is obtained historically. Recall bias can be a major problem in these types of studies if patients are contacted directly and the interviewers are not blinded to the patient group assignment, especially for the cases (Sedgwick 2011a).

In a case-control study, the investigator decides how many subjects with the disease (cases) and without the disease (controls) to study so the proportion of cases and controls are not reflective of a specific population. Therefore, incidence rates and absolute or relative risk of the disease cannot be calculated. Because this type of study examines the odds of exposure in cases versus controls, the only measure of association of effect that can be calculated from a case-control study is the odds ratio. This is the ratio of odds of the exposure in the cases compared with the odds of the exposure in the controls (Sedgwick 2013b).

Critical Appraisal of Case-Control Studies in Clinical Practice

Critical appraisal of case-control studies focuses a great deal on aspects related to the exposure of interest because the groups are created by whether they have the outcome

of interest (cases) or not (controls), and then each group is examined for exposures of interest. Appraisal of case-control studies includes determining whether the study groups are balanced for baseline characteristics that are prognostic for the exposure of interest. This is different than in cohort studies, where study groups are examined for balance of baseline characteristics prognostic for the outcome of interest. Clinicians should assess for whether there are baseline differences in the opportunity for the exposure and whether the investigators conducted statistical adjustment methods. In case-control studies, matching and multivariable regression are typical statistical adjustment methods. Also, it is important to examine whether the exposure occurred before the outcome, and whether the exposure is measured in a consistent way between groups. Similar to cohort studies, it should be determined whether there was complete and sufficiently long enough follow-up for the outcome of interest, and when examining the results, to check for a dose-response gradient in the relationship between exposure and outcomes that would strengthen the association (Sedgwick 2013f, 2013b; Guyatt 2014).

Cardiology Example of Case-Control Study

A study examining the association between antibiotics and antifungals with bleeding in patients taking warfarin will be used as an example of the case-control study (Table 2-4).

It is important to note that confounding is a specific concern in case-control studies. In this study, the authors used both matching and multivariable logistic regression to balance the baseline characteristics that strengthens their methods and reduces potential confounding. We can

Table 2-4. Critical Appraisal of Antibiotic/Antifungal and Warfarin Case-Control Study

Population	Patients taking warfarin
Intervention/Exposure	Antibiotics/antifungals while taking warfarin
Cases (with outcome)	Hospitalized with primary diagnosis of bleeding
Controls (without outcome)	No bleeding hospitalization
Study Type	Case-control study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/ Possible	High
Cases and controls have similar opportunity for exposure	Well matched for exposure EXCEPT increased comorbidity and nursing home in cases; matching and logistic regression were used to balance baseline differences in opportunity for exposure; controls were matched on index month of bleeding event in cases to allow similar dates in cases and controls	x		
Exposures measured in similar method in both groups	Exposure measured same in both groups using Medicare Part D prescription claims	x		
Exposure preceded outcome	Although it is sometimes difficult to determine in a case-control study, in this study, the health records show that exposure to antibiotic occurred before bleeding hospitalization	x		
Dose-response gradient	There was a dose response gradient based on timing of exposure with adjusted ORs as follows: Antibiotic use 0–15d pre–event: 2.37 (1.75–3.22) 15–60d pre–event: 2.11 (1.50–2.97) >60d pre–event: 1.25 (0.78–2.01)	x		

Exposure	Case Exposure (n=798)	Control Exposure (n=2394)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Any antibiotic	170	264	2.18 (1.77–2.70)	2.01 (1.62–2.50)
Cotrimoxazole	22	22	3.06 (1.68–5.55)	2.70 (1.46–5.05)
Azole antifungal	8	17	6.49 (2.79–15.10)	4.57 (1.90–11.03)

Information from: Baillargeon J, Holmes HM, Lin YL, et al. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012;125:183-9.

confirm that there was confounding because we can see that the adjusted odds ratios are lower than the unadjusted or crude odds ratios. There is still the possibility of residual confounding. However, the odds ratios are all moderate to large in size, and even with residual confounding, there is still likely an association between antibiotic exposure and bleeding in patients taking warfarin. Therefore, we can state that the odds of exposure to antibiotics is increased in those who had bleeding (cases) compared with those who

did not have bleeding (controls). Specifically, cotrimoxazole and azole antifungals had some of the highest odds ratios in this study.

Value of Study Type in Clinical Practice

Case-control studies are especially valuable for evaluating adverse drug reactions, especially rare adverse effects or ones with a long latency period. Case-control studies have less risk of confounding if they are nested within a common

population and use one or more statistical methods to adjust for potential confounding.

NOVEL OBSERVATIONAL STUDY DESIGNS

Novel observational study designs include propensity score-matched methods (propensity score-matched cohort studies, inverse probability of treatment weighting propensity score studies), propensity score-adjusted analysis studies, case-crossover studies, and instrumental variable analysis studies.

Data sources for novel observational studies are similar to traditional observational designs, and include medical records, administrative databases, clinical data bases, and clinical registries. The use of population-based databases reduces sampling bias and improves generalizability.

Propensity Score Methods

Propensity score methods studies have been increasingly used in the cardiology literature because randomized controlled trials are often not feasible or ethical to answer certain questions of harm or questions of effectiveness of interventions in diverse, general populations. In an observational study, an imbalance in baseline characteristics between the control and treatment groups can lead to a biased estimate of the treatment effect caused by confounding. Common statistical design approaches such as matching, stratification, and regression models are used to adjust for these baseline differences but are often limited by the number of confounding variables that can be accommodated.

Propensity score methods, as developed by Rosenbaum and Rubin, have gained popularity because they are able to reduce confounding bias without being limited to a small number of covariates in the model. The propensity score (from 0 to 1) is the conditional probability that a subject will be assigned to the treatment group based on baseline characteristics. The score, which is estimated using a logistic regression model, can be thought of as a balancing score, similar to randomization that attempts to balance the covariates between 2 groups. Variables that affect the outcome of interest are the ones that should be included in the logistic regression model estimating the propensity score. In patients with the same propensity score, the baseline characteristics between the two groups should be similar (Rosenbaum 1983).

There are four main propensity score methods: propensity score-matching, inverse probability of treatment weighting methods, propensity score adjustment methods, and stratification by the propensity score methods. This chapter covers the first three methods, which are more commonly used. Table 2-5 summarizes the positive and negative attributes of each of these three study designs.

Propensity Score-Matched Cohort Studies

Description, Advantages and Disadvantages of Study Design

Propensity score-matched cohorts most closely resemble the framework of a randomized controlled trial. In propensity score-matching, patients with similar propensity scores in the treatment and control groups are matched. Ideally, only patients with the exact same propensity score would be matched, but in practice this is rarely possible. Instead, control participants are selected if their propensity score is considered close enough to be matched to be treated subject, using methods such as nearest neighbor matching within a specified range of values (often called *caliper distance*). Once the matched samples are formed, the treatment effect can be estimated by directly comparing outcomes between the treatment and control groups, similar to a randomized controlled trial. However, statistical analyses that account for a matched design must be used.

Propensity score-matched cohort designs are transparent in their methods. Their structure most closely resembles a randomized controlled trial. The outcomes between treatment and control groups can be directly compared, making these studies the easiest of the propensity score method studies for a clinician to examine. These propensity score-matched studies are superior at reducing bias versus traditional covariate adjustment methods and the propensity score-adjusted methods.

A disadvantage is that if matches are not found between the control and treatment patients, some of the treated patients may be excluded from the final matched sample, resulting in lower generalizability of the results. In addition, it is necessary to have more control subjects to choose from than treated subjects, so that control subjects can be match to those treated.

Critical Appraisal of Propensity Score-Matched Cohort Studies in Clinical Practice

Because propensity score-matched cohort studies are cohorts, the critical appraisal criteria noted in the cohort section apply to these studies. However, the method for determining if the baseline characteristics are balanced differs slightly. Typically, in these studies, there is a table that compares baseline characteristics between groups before propensity matching is conducted, showing the p value differences – similar to that usually shown in a cohort study. However, for a propensity-matched cohort, the clinician must also assess a second baseline characteristic table that is created after propensity score matching is conducted. Two aspects should be examined in this second table. First, there will be a column entitled standardized differences. The clinician should examine for whether the stated differences are all less than 0.1 because this indicates a good balance between groups for that baseline covariate. If there are differences of 0.1 or greater, it is questionable whether the authors have been able to create a balanced cohort using propensity score-matching methods. The authors should explain why there are

Table 2-5. Comparison of Propensity Score Method Cohort Studies

Characteristic	Propensity Score-Matched	Inverse Probability of Treatment Weighting	Propensity Score-Adjusted
Positive Attributes			
Transparent	x		
Selection bias reduction	Reduced greatly	Reduced greatly	Less reduction
Baseline covariates of treated and control groups easily described and presented.	x	x	
Simple absolute and relative measures of effect can be reported	x	x	
Presentation of analyses and results similar to RCTs	x	x	
Produces OR and HR estimates	x	x	x
Uses all data		x	x
Negative Attributes			
“Black box” methods		x	x
Excludes unmatched control participants	x		
Requires more control than treated subjects	x		
No clear distinction between design and analysis phase			x
Outcome always in sight so temptation towards an anticipated model is present			x

Information from: Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. *Am J Epidemiol* 2006;163:1149-56; and Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. *Can J Cardiol* 2016;32:259-65.

still imbalances, and whether they have tried other methods, such as adding interaction terms, or further adjusting these variables using multivariable regression. The second aspect to examine is the changes in sample size listed in the initial table before matching and the table after matching. A larger difference in the sample sizes, especially more than a 25% decrease in the sample, might indicate less generalizability to a real world population.

Another advantage of propensity score-matched cohorts is the ability to easily determine absolute measures of effect size (absolute risk differences, numbers needed to treat and harm) in addition to relative differences (relative risk, hazard ratio), similar to how one would calculate these values from a randomized controlled trial (Brookhart 2006; Deb 2016).

Cardiology Example of Propensity Score-Matched Cohort Study

Table 2-6 describes a study comparing brand versus generic atorvastatin in acute coronary syndrome patients as an example of a propensity-score matched cohort study.

In this study, 81% of the treated patients were matched with control patients, which is a good level of matching for

generalizability. All standardized differences were less than 0.1, which represents good balance of all the baseline characteristics between groups. Therefore, the study has a comparatively low risk of bias for this type of observational study. Given the propensity score-matched methods, actual event rates can be calculated directly without further adjustments being required. From the efficacy results, we see that there is no difference between groups with narrow confidence intervals. Because there is no statistical difference between groups, we do not calculate number needed to treat or number needed to harm.

Value of Study Type in Clinical Practice

As stated earlier, one of the largest values of cohort studies is the ability to examine harms in the clinical practice setting or a population-based setting that cannot be performed with randomized controlled trials. Propensity score-matched cohort studies are especially useful when there are large enough sample sizes to do suitable matching that results in very well-balanced characteristics between groups. They are easy to understand for clinicians and measures of treatment effect can be calculated directly without further adjustment required.

Table 2-6. Critical Appraisal of Generic Atorvastatin Propensity Score-Matched Cohort Study

Population	Patients with acute coronary syndromes, discharged alive
Intervention/Exposure	Generic atorvastatin within 7 days post-ACS
Comparison	Brand atorvastatin within 7 days post-ACS
Outcome	Death, recurrent MI/unstable angina
Study Type	Propensity score-matched cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Groups similar at baseline or statistical adjustment	There were some baseline differences in patient characteristics before propensity matching; there were 81% of patients matched successfully using the propensity score; after the propensity matched cohort was created, the 2 groups were well-balanced as shown by a standardized difference <0.1 for all variables	x		
Exposure precedes outcome	Universal drug benefit records ascertained exposure and determined the timing before the outcome	x		
Outcomes measured similarly in groups	Administrative records were used to consistently capture outcome events similarly in both groups	x		
Follow-up complete and long enough	1-year follow-up of outcomes was long enough for recurrent events post-ACS and follow-up was complete	x		
Dose-response gradient	Not applicable	Not applicable		

Type of Outcome	Outcome	Brand Risk (n=7863)	Generic Risk (n=7863)	Hazard Ratio (95% CI) p-value	Absolute Risk Difference	NNT/NNH
Efficacy	Death/recurrent ACS	17.7%	17.7%	1.00 (0.93-1.08) 0.94	0%	N/A
Safety	Diabetes	1.9%	2.0%	Not provided	0.1%	N/A

Information from: Jackevicius CA, Tu JV, Krumholz HM, et al. Comparative effectiveness of generic atorvastatin and Lipitor in patients hospitalized with an acute coronary syndrome. *J Am Heart Assoc* 2016;5:e003350.

Decision Scenario

A propensity score-matched cohort study was conducted to examine the association between exposure to a macrolide antibiotic and torsades de pointes. The investigators compared the rate at which torsades de pointes

occurred in patients dispensed macrolide versus cephalosporin antibiotics. What aspects are important for the clinician to consider when examining the methods?

ANSWER

All of the usual critical appraisal criteria apply to propensity score-matched cohort studies. These include: determining if the study groups are balanced for baseline characteristics that are prognostic for the outcome, whether the exposure occurred before the outcome, whether the outcome is measured in a consistent way for all groups, and whether there was complete and sufficiently long enough follow-up. In addition, the baseline

characteristics table must be examined after matching has been completed to determine if standardized differences for each covariate are less than 0.1 to indicate good balance between groups. Finally, the sample size before and after matching should be examined to determine what proportion of treated patients could not be matched to controls. A greater proportion of matching results in higher degree of generalizability.

1. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. *Am J Epidemiol* 2006;163:1149-56.
2. Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. *Can J Cardiol* 2016;32:59-65.

Inverse Probability of Treatment Weighting Propensity Score Cohort Studies

Description, Advantages, and Disadvantages of Study Design

Another way of using the propensity score is for the investigator to create a weight based on the score itself. This method, called inverse probability of treatment weighting (IPTW), creates a synthetic sample in which the measured baseline characteristics are distributed independent of treatment assignment. These weights are similar to weighted survey samples that allow a sample to be representative of a specific population. The weight of the subject is equal to the inverse of the probability of receiving the treatment that the subject actually received. In a treated cohort, treated subjects with lower propensity scores; that is, they are less likely to receive treatment but actually do get treatment, receive a higher weight compared with treated subjects with higher scores. Conversely, control participants who are more likely to receive the active treatment because of a higher propensity score, receive a higher weight. Once the weights are calculated for each subject, these weights are incorporated in further analyses that compare outcomes between the treatment groups (Brookhart 2006; Deb 2016).

Similar to propensity score-matching methods, advantages of IPTW include presenting analyses and results similar to that of a randomized controlled trial and superiority in reducing bias compared with covariate-adjustments methods. Furthermore, IPTW also uses all available data, increasing generalizability. This study design can also be used when there are unequal sample sizes between groups, and it is not necessary to have more controls than treated patients. The primary disadvantage of IPTW methods is that they are not as transparent as propensity-score matching methods, and may not be as easily understood by clinicians.

Critical Appraisal of IPTW Cohort Studies in Clinical Practice

For IPTW cohort studies, the critical appraisal criteria noted in the cohort section above also apply. In addition, IPTW studies have some similar critical appraisal criteria as propensity-score matched cohort studies. Specifically, evaluation of baseline characteristics is a two-step procedure. The reader must examine the baseline characteristics in the study population both before as well as after the IPTW process is completed and assess for balance. Before the IPTW, many baseline characteristics are seen to be imbalanced between groups. One should then examine the baseline characteristic table after the IPTW process and examine the standardized differences for each baseline characteristic. Similar to propensity-score matched cohorts, standardized differences less than 0.1 indicate a good balance for that characteristic. Should any standardized differences be 0.1 or greater, the investigator should indicate further methods to balance these residual differences. Also similar to propensity

score-matched cohorts, IPTW cohort studies can generate actual event rates that do not require further adjustment, and thus, can be used to directly calculate absolute risk differences (Brookhart 2006; Deb 2016).

Cardiology Example of IPTW Cohort Study

Table 2-7 describes an IPTW cohort study that examined the association between β -blocker use before out-of-hospital cardiac arrest on the outcome of mortality at 30 days.

This study used suitable IPTW methods to balance baseline characteristics between groups. However, there remained some imbalances in certain characteristics, so the investigators added these as model covariates, which did not alter the primary findings, making them robust. Because there was no significant difference between groups, the numbers needed to treat and to harm were not calculated.

Value of Study Type in Clinical Practice

The value of the IPTW propensity-score cohort studies is similar to that of propensity-score-matched cohort studies. However, unlike in propensity score-matched studies where matching results in equal sample sizes in the two groups, in IPTW studies, because no patients are excluded, unequal study group sizes are possible but do not limit this study design. The methods for this study design are not as transparent as the propensity-score-matched cohort studies, making them less easy for a reader to interpret.

Propensity Score-Adjusted Analysis Cohort Studies

Description, Advantages and Disadvantages of Study Design

In propensity score-adjusted analysis studies, the propensity score is simply used in an adjustment regression model as a covariate. When using propensity score-adjusted methods, once propensity scores are generated for each patient, the outcome variable and the exposure variable of interest, along with propensity score as a covariate are entered into a regression model to generate an adjusted treatment effect. Other covariates may also be added to the model for further adjustment.

The main advantages of propensity score-adjusted analysis studies are that they use all of the data available from all patients in treatment and control groups, and a large number of confounders can be used to generate the propensity score itself, rather than needing to add all of these confounders into the regression model directly.

Propensity score-adjusted methods have more disadvantages than other propensity-score methods. Because there is no distinction between the design and analysis phases, and because the methods are not transparent, a clear balanced cohort that can be examined is not created. This method only produces adjusted odds and hazard ratios rather than incidence and event rates per group; therefore, directly calculating unadjusted absolute and relative risk differences is not possible.

Table 2-7. Critical Appraisal of β -Blocker and Cardiac Arrest IPTW Cohort Study

Population	Patients with out-of-hospital cardiac arrest
Intervention/Exposure	β -blocker use within 90 days before cardiac arrest
Comparison	No β -blocker use
Outcome	Mortality in 30 days post-arrest
Study Type	IPTW cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Groups similar at baseline or statistical adjustment	The authors used the combination of a cardiac arrest registry with administrative data for addressing potential confounders; the groups had significant baseline differences that were mostly balanced as shown by standardized differences <0.1 after the IPTW weighting was applied; the remaining differences in cardiac testing, pacemaker, and medication use were addressed by adding these variables as model covariates did not alter the study results or conclusions		x	
Exposure precedes outcome	From administrative data it was clear that exposure preceded outcome	x		
Outcomes measured similarly in groups	Mortality was measured in the same method in both groups	x		
Follow-up complete and long enough	30-day all-cause mortality is long enough follow-up; follow-up was complete	x		
Dose-response gradient	Not applicable	N/A		

Type of Outcome	Outcome	No β -blocker Risk (n=5355)	β -blocker Risk (n=2911)	Relative Risk (95% CI) p value	Relative Risk Difference	Absolute Risk Difference	NNT/NNH
Safety	Mortality	95.1%	95.6%	0.995 CI not provided p=0.36	RRI: 0.5%	ARI 0.5%	N/A

Information from: Czarnecki A, Morrison LJ, Qiu F, et al. Association of prior β -blocker use and the outcomes of patients with out-of-hospital cardiac arrest. *Am Heart J* 2015;170:1018-24.e2.

Critical Appraisal of Propensity Score-Adjusted Cohort Studies in Clinical Practice

Propensity score-adjusted cohort studies are evaluated more similarly to traditional retrospective cohort studies than they are to propensity score-matched or IPTW cohort studies. This is because propensity score-adjusted cohort studies simply add the propensity score to their regression model as an additional covariate—there are not two separate baseline characteristic tables to examine. Furthermore, the event rates are crude event rates and do not take into account the balancing that is done with the regression model to produce the adjusted hazard ratio or relative risk. Therefore, readers must use the adjusted hazard ratio and not the crude event rates in order to generate the NNT or NNH. This method of

calculating NNT or NNH is a bit more complex but can be done with online calculators such as the one at [KT Clearinghouse website](#) (Brookhart 2006; Deb 2016).

Cardiology Example of Propensity Score-Adjusted Cohort Study

Table 2-8 describes a propensity score-adjusted cohort study of bleeding and thrombosis outcomes in patients who either resumed or did not resume warfarin after a GI bleed.

In this study, the investigators added the propensity score to their adjustment model, which contains all relevant variables except for the site of bleeding. From the crude relative risk we calculated, we can see a large difference in the adjusted hazard ratio for GI bleeding, indicating that significant confounding

Table 2-8. Critical Appraisal of Warfarin Resumption after GI Bleed Propensity Score-Adjusted Cohort Study

Population	Patients who developed GI bleeding on warfarin
Intervention/Exposure	Warfarin resumption
Comparison	No warfarin resumption
Outcome	GI bleeding, thrombosis, and death
Study Type	Propensity score-adjusted cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Groups similar at baseline or statistical adjustment	Groups not similar at baseline (warfarin resumers were younger, with more prosthetic valve, less HTN, more rectal bleeding); authors added propensity score to adjustment model; propensity score contains all variables that were different except site of bleeding; unadjusted estimates not provided to be able to determine amount of change in estimate after adjustment, although it was possible to calculate crude relative risk		x	
Exposure precedes outcome	Kaiser administrative data was used to ascertain that exposure preceded outcome; all patients needed to have Kaiser membership for 180 days before index event to ensure capture of data	x		
Outcomes measured similarly in groups	Outcomes measured similarly using Kaiser electronic data with confirmation via manual medical record review independently by two investigators	x		
Follow-up complete and long enough	All patients needed to have Kaiser membership for 180 days before index event to ensure complete capture of data; 90 days is long enough to capture most relevant recurrent bleeding and thrombosis related to interruption of therapy	x		
Dose-response gradient	Timing-response gradient demonstrated; patients who never interrupted or resumed warfarin within 14 days had no thrombosis vs. later resumption; GI bleeding recurrence was increased when warfarin was resumed within 1 to 7 days after index bleed vs. later	x		

Type of Outcome	Outcome	Crude No Warfarin Resumption Risk (n=182)	Crude Warfarin Resumption Risk (n=260)	Crude Absolute Risk Difference	Crude Relative Risk	Adjusted Hazard Ratio (95% CI) p value	Adjusted Relative Risk Difference	NNT/ NNH
Efficacy	Thrombosis	5.5%	0.4%	ARR: 5.1%	0.07	0.05 (0.01-0.58) P<0.001	RRR: 95%	NNT: 20
Efficacy	Death	Not provided			N/A	0.31 (0.15-0.62)	RRR: 69%	N/A
Safety	GI Bleeding	5.5%	10.0%	ARI: 4.5%	1.82	1.32 (0.50-3.57) P=0.09	RRI: 32%	N/A

Information from: Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for GI tract bleeding. Arch Intern Med 2012;172:1484-91.

was accounted for. There is minimal difference between the crude relative risk and the adjusted hazard ratio for thrombosis, indicating a relatively stable estimate of thrombosis risk avoided with warfarin resumption. Given the small sample size of the study, confidence intervals around the treatment effects are imprecise. Despite these limitations, there was a large absolute risk reduction of thrombosis with warfarin resumption that translates into a number needed to treat of 20 patients to prevent one thrombosis event.

Value of Study Type in Clinical Practice

The value of propensity score-adjusted cohort studies is similar to that of traditional retrospective cohort studies. The propensity score adjustment does help with adjusting many more variables than is possible in a traditional cohort study, strengthening the adjustment for confounding. However, these propensity score methods are less transparent than other designs.

Exposure-Crossover (Case-Crossover) Cohort Studies

Description, Advantages, and Disadvantages of Study Design

A case-crossover design only involves cases and may be used when a brief exposure causes a temporary change in the risk of a rare, acute-onset disease. This type of study design resembles an experimental crossover study in that the same subject is assessed during two or more periods. However, in the case-crossover design, subjects are examined for the risk of exposure during the time periods rather than for the outcome (Figure 2-3). The case period is most proximal to the outcome or event of interest, and each subject serves as their own control during earlier periods. This design also assumes that the effect of the exposure is not cumulative, that the exposure does not have a carryover effect, and that the outcome of interest does not influence the exposure.

Self-matching of cases reduces confounding and selection bias and increases efficiency of the study. It may require

a smaller sample size because of the crossover nature of the study and decreased between-subject variability.

Disadvantages, particularly in cardiovascular studies, are that many exposures are not transient, and many of the outcomes evaluated have long onsets and may be fatal. The outcome of interest or the event must be a discrete event. In this type of study design, patients must be alive for the period during exposure and during the period of non-exposure. It may also be difficult to ascertain when the exposure actually took place, particularly when relying on patient recall or administrative data records.

Critical Appraisal of Case-Crossover Cohort Studies in Clinical Practice

Case-crossover cohort studies are evaluated in most ways similar to traditional cohort studies, along with additional critical appraisal criteria because of the unique nature of this study design. The additional criteria include determining whether the exposure is transient, whether there is a carryover effect for the exposure between periods, and when evaluating whether case and control periods have similar opportunity for exposure, determining whether the characteristics of the cases may have changed over time (Brookhart 2010; Delaney 2009; Maclure 1991).

Cardiology Example of Case-Crossover Cohort Study

As the example of a case-crossover study, Table 2-9 presents a trial that examines the risk of antihypertensive drug initiation during various time periods before patients experienced a serious fall injury.

In this case-crossover study, the risk of bias appears to be low in general. However, given the long look-back timeframe, it is possible the patient characteristics may have changed between the case period and the control periods. The odds ratios show a small to moderate magnitude of harm with antihypertensive therapy initiation, addition, and titration in relation to a serious fall injury.

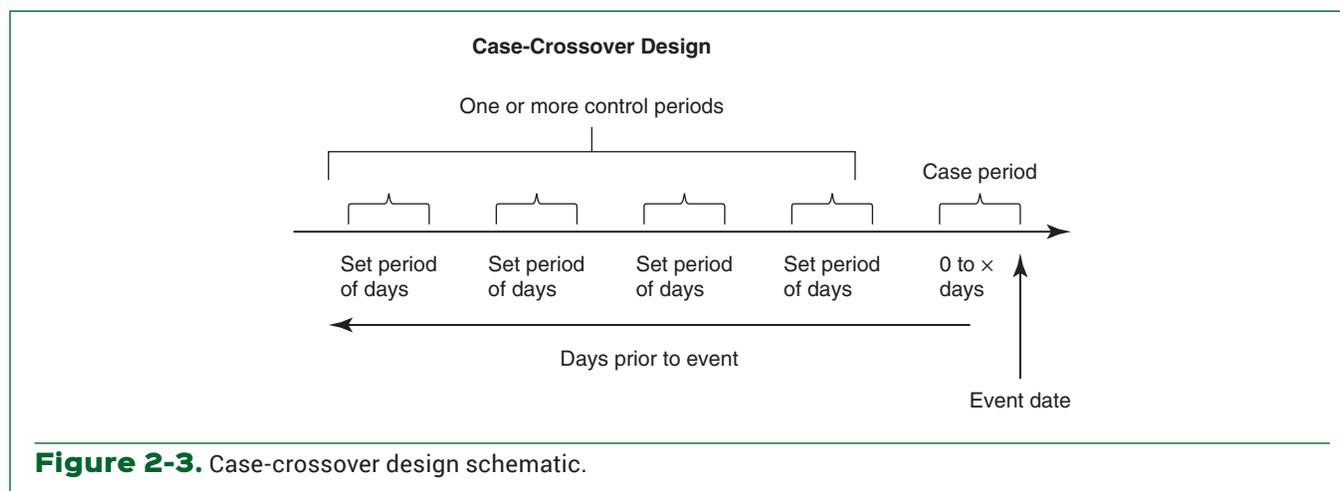


Figure 2-3. Case-crossover design schematic.

Table 2-9. Critical Appraisal of Antihypertensive Drug and Fall Risk Case-Crossover Study

Population	Medicare patients with a serious fall injury
Intervention/Exposure	Antihypertensive drug initiation
Case period (with exposure)	Antihypertensive drug initiation within 14 days before fall
Control periods (exposure at differing intervals ≥ 30 days preceding fall)	Antihypertensive drug initiation ≥ 30 days before fall
Study Type	Case-crossover cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Exposure transient in nature	The antihypertensive effect of the medications is transient in nature rather than permanent	x		
Carryover effect	There is no or minimal cumulative or carryover effect between periods	x		
Case and control periods have similar opportunity for exposure	Likely well matched for opportunity for exposure because same patients are in the case period and the control periods and these periods are relatively close to each other; however, because the control periods go back to 194 days before the case period, it is possible that there were some changes in clinical characteristics during this period; if new conditions appeared during the later (case period), patients may be more prone to be exposed to antihypertensive therapies		x	
Exposures measured in similar method in both groups	Exposure measured same in both groups using Medicare Part D Rx claims	x		
Exposure preceded outcome	Exposure to the antihypertensive occurred before serious fall injury hospitalization because the study only looked retrospectively at use pre-fall event	x		
Dose-response gradient	There was a recency of exposure response gradient based on timing of exposure with adjusted ORs estimated by authors in a sensitivity analysis as follows: Case period varied by these definitions: <ul style="list-style-type: none"> • 0–14d pre-event: 1.36 (1.19–1.55) [6 control periods between 30–44 and 180–194 days] • 30–44d pre-event: 1.01 (0.86–1.17) [5 control periods between 60–74 and 180–194 days] • 60–74d pre-event: 0.97 (0.83–1.13) [4 control periods between 90–104 and 180–194 days] • 90–104d pre-event: 1.00 (0.85–1.17) [3 control periods between 120–134 and 180–194 days] All control periods preceded the case period	x		

Exposure ^a	Case Period Exposure	Control Periods Exposure	Unadjusted Odds Ratio (95% CI)
Antihypertensive initiation ≤ 15 days before fall	272 (0.30%)	1201 (0.22%)	1.36 (1.19–1.55)
Antihypertensive addition ≤ 15 days before fall	1508 (1.67%)	7820 (1.45%)	1.16 (1.10–1.23)
Antihypertensive titration ≤ 15 days before fall	3113 (3.45%)	16714 (3.09%)	1.13 (1.08–1.18)

^a90,127 patients experienced serious fall injuries and were the subjects of interest in the study.

Information from: Shimbo D, Barrett Bowling C, Levitan EB, et al. Short-term risk of serious fall injuries in older adults initiating and intensifying treatment with antihypertensive medication. *Circ Cardiovasc Qual Outcomes* 2016;9:222-9.

Value of Study Type in Clinical Practice

The case-crossover study design is most valuable when examining transient exposures that may temporarily change a patient's risk for an event. In cardiovascular disease, some of these criteria are difficult to meet.

Instrumental Variable Analysis Cohort Studies

Description, Advantages and Disadvantages of Study Design

Although randomized controlled trials are the gold standard for comparing treatment effects between groups, it is not always ethical or possible to conduct them. Therefore, observational studies are often conducted instead. In observational studies, patients receiving treatment may differ from untreated patients in prognostic variables that affect the outcome. Thus, differences in outcomes are related to both the effects of the treatment and the effects of the patient's prognostic variables. Observational studies use multiple statistical adjustment techniques to attempt to balance these prognostic variables. An alternative to traditional statistical adjustment techniques and an alternative to randomization is the use of instrumental variables which are thought to act like a "natural randomization" of patients to varying treatment intensities, rather than 0% (control) and 100% (intervention) as in randomization.

Instrumental variable analysis has become a more popular technique in observational studies. The challenge in these studies is to find an instrument that can be used as the instrumental variable. There are five assumptions that are required for instrumental variable analysis, however, these can be difficult to verify in practice. These assumptions include potential outcomes for each patient are unrelated to the treatment status of other patients; the instrument affects receipt of the treatment of interest; the effect is always in the same direction; the instrument assigns treatment randomly; and the instrument has an effect on the outcome only through the treatment assignment.

There are four common instrument categories that are typically used in these studies: distance to facility, regional variation, facility variation, and physician variation. To illustrate, an example of relative distance to hospitals as the instrument in the situation of estimating the effect of mortality with use of cardiac catheterization after myocardial infarction is used. The researchers would classify each hospital in the study as a catheterization or non-catheterization hospital, then patients are assigned a value based on whether they live closer to a catheterization hospital or non-catheterization hospital. Those patients living closer to a catheterization hospital are assumed to be more likely to receive an angiogram. Similar to random assignment, the instrumental variable analysis using a relative distance to hospital assumes the relative distance between a patient's place of residence and a catheterization hospital predicts

treatment choice that is independent of all characteristics that usually confound the relationship between treatment and outcomes. For example, characteristics such as age, comorbidity, and baseline drugs are considered unrelated to the relative distance between a patient's residence and a catheterization hospital. It should be noted that the instrumental variable analysis represents the adjusted treatment effect in the so-called "marginal patient". In the above case, the marginal patient would represent a subset of borderline patients, those that would receive catheterization in the higher intensity (catheterization hospitals) but not at a lower intensity (non-catheterization) hospital.

The results of instrumental variable analysis may be biased if the instrument and outcome are related through an unadjusted third variable, an "instrument-outcome confounder". For the distance to facility instrument, potential confounders include geographic location, patient characteristics, treatment characteristics, and facility characteristics (Garabedian 2014).

If a suitable instrument is found for a particular study, instrumental variable analysis can closely mimic random treatment assignment and balance known and unknown confounders. This creates less-biased estimates of treatment effect. However, it is often difficult to find a suitable instrument that can practically be used in many study situations. It can also be difficult to verify all of the five assumptions underlying instrumental variable analysis.

Critical Appraisal of Instrumental Variable Analysis Cohort Studies in Clinical Practice

A reader of instrumental variable analysis should attempt to see if the five assumptions are met; for the specific instrument category used as the instrumental variable, it should be determined whether the investigators have addressed or attempted to reduce potential confounding. In addition, the other critical appraisal criteria for a traditional cohort studies continue to apply to instrumental variable analysis studies.

Cardiology Example of Instrumental Variable Analysis Cohort Study

Table 2-10 describes a study evaluating the risk of mortality and ICU admission in older patients with pneumonia as an example of an instrumental variable cohort study.

Although some of the assumptions about the instrument are difficult to verify in practice, this is the case with many instrumental variable studies. The instrumental variable of distance to facility chosen for this study appears to be a very suitable instrument that would mimic a natural randomization. This study would be strengthened by adding confidence intervals to determine the precision of the treatment estimate.

Value of Study Type in Clinical Practice

Instrumental variable studies can mimic the randomization process in randomized controlled trials if a suitable

Table 2-10. Critical Appraisal of ICU Admission and Mortality in Pneumonia Instrumental Variable Analysis Cohort Study

Population	Older patients with pneumonia
Intervention/Exposure	ICU admission
Comparison	No ICU admission
Outcome	Mortality at 30 days
Study Type	Instrumental variable cohort study

Criteria	Description/Comment	Risk of Bias		
		Low	Slight/Possible	High
Instrumental variable assumptions	The choice of distance to facility clearly meets two criteria: distance correlated with ICU admission, and distance only has impact on mortality outcome through the ICU admission (not directly); assumptions 1, 3, and 4 are difficult to verify in practice		x	
Groups similar at baseline or statistical adjustment for confounders	Although there were differences in baseline characteristics, the investigators adjusted for extensive patient, treatment, geographic and hospital characteristics that could be potential instrument-outcome confounders	x		
Exposure precedes outcome	Exposure precedes outcome	x		
Outcomes measured similarly in groups	Outcomes were measured the same in both groups using mortality data in the Medicare Beneficiary Summary File	x		
Follow-up complete and long enough	30-day follow-up is a reasonable follow-up duration to assess acute mortality related to pneumonia; follow-up was complete	x		
Dose-response gradient	Not applicable	N/A		

Type of Outcome	Outcome	Relative Risk (95% CI) p value	Relative Risk Difference	No ICU Admission Risk (n=783990)	ICU Admission Risk (n=328404)	Absolute Risk Difference	NNT/NNH
Efficacy	Mortality	0.72 CI N/A p=0.02	RRR: 28%	20.5%	14.8%	ARR: 5.7%	18

Information from: Valley TS, Sjoding MW, Ryan AM, et al. Association of intensive care unit admission with mortality among older patients with pneumonia. JAMA 2015;314:1272-9.

instrumental variable can be found to act as a natural randomization process for the study question of interest. Finding a suitable instrument is often quite difficult, therefore, there are few instrumental variable studies published in the cardiology literature.

CONCLUSION

There are many diverse study designs beyond randomized placebo-controlled trials that are available to answer clinical questions relevant to cardiology. Each specific study

design has its own unique advantages and disadvantages. Pharmacists play a key role in understanding and evaluating the risk of bias, interpreting the results, and considering the generalizability of these various study types. Pharmacists can use their skills in critical appraisal to select the optimal evidence-based therapies that aim to provide treatments with the best clinical outcomes evidence for patients. Pharmacists can also assist others in the healthcare team by developing their critical appraisal skills and teaching others how to evaluate diverse study designs using a practical, clinically-applicable framework.

Practice Points

- Many study designs exist beyond randomized placebo controlled trials. These study designs require different critical appraisal tools.
- Active-control, superiority trials and noninferiority trials are effective study designs when placebo controls are not a suitable option, particularly when a gold standard therapy exists in practice and would be the most suitable comparison.
- While noninferiority trials are randomized controlled trials, they require modified appraisal due to the possibility that traditional RCT design biases towards noninferiority. These additional criteria include: both ITT and PP analysis, assessment of whether the standard treatment effect was maintained, and close examination of a clinically relevant noninferiority margin.
- Traditional and novel observational study designs require careful assessment for potential confounding which is the biggest limitation of this type of study design.
- Observational study designs can assist clinicians with examining important clinical questions when randomized controlled trials are not possible. Of course, examination for confounding is a necessary part of appraising an observational study.
- In cohort studies, examination for baseline differences between groups for characteristics that might impact prognosis for the outcome, and methods that balance or minimize these differences is key for assessing risk of bias.
- In case-control studies, assessment for baseline characteristics that might impact the opportunity for the exposure of interest is one of the key critical appraisal elements.
- In all observational studies, a reader must examine whether the exposures and outcomes were measured in similar ways for all study groups.
- In propensity score-matched cohort studies and IPTW cohort studies, the reader must examine baseline characteristics both before and after the propensity-score techniques have been applied.
- In case-crossover studies, it is important to determine if the exposure is transient and suitable for this type of study design.
- In instrumental variable analysis studies, it is important to check the assumptions of the instrumental variable and examine for potential instrument-outcome confounders.

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Self-Assessment Questions

21. You are searching for a study to answer your clinical question about whether a 2-year duration of dual antiplatelet therapy is superior to a 1-year duration to prevent death or recurrent myocardial infarction post-acute coronary syndrome. Which one of the following study designs and rationale is least biased and most appropriate to answer your clinical question?
- Retrospective, cohort study: study of rare adverse events
 - Randomized, active-control trial: reduced selection bias
 - Randomized, noninferiority trial: ability to compare to placebo
 - Propensity score-matched cohort study: low external validity
22. You are reading a paper that is investigating a new anti-hypertensive drug using a randomized active-control superiority trial design for uncomplicated hypertension. Which of the following regimens would be the best control arm based on the use of guideline standards?
- Hydralazine 10 mg three times daily
 - Atenolol 25 mg daily
 - Placebo once daily
 - Hydrochlorothiazide 25 mg daily
23. A randomized active-control superiority trial has been conducted in 20,000 patients with hypertension, and it finds a significantly lower rate of stroke with the novel therapy (4% vs. 5%, $p < 0.01$). In evaluating the study, you note that concealment of the randomization list is unclear, it is open label, per protocol analysis is conducted, 10% of patients have missing outcome data, and baseline characteristics are not similar between groups. What level of risk of bias does this trial have?
- Very low risk
 - Low risk
 - Moderate risk
 - High risk
24. A noninferiority trial is conducted that compares warfarin to another new direct oral anticoagulant for atrial fibrillation for stroke prevention. Which one of the following regimens would be the best gold standard comparison arm for this trial?
- Warfarin with target INR 2.5–3.5
 - Warfarin plus aspirin 325 mg daily
 - Warfarin with mean time in therapeutic range 62%–68%
 - Warfarin with mean time in therapeutic range 55%
25. Which of the following statements about a novel therapy best justifies the conduct of a noninferiority trial?
- It is expected to be more expensive.
 - It is expected to be less safe.
 - It is expected to be more effective.
 - It is expected to be more convenient.
26. A noninferiority trial compared a new anticoagulant with warfarin for stroke prevention in atrial fibrillation; results were HR 1.10 (95% CI, 0.90–1.30). The noninferiority margin set by the authors was a HR of 1.46. This margin means that up to 46% more strokes would be within the range of treatment estimates considered noninferior with the new anticoagulant. Which of the following best interprets this trial according to the NI margin set by the study?
- Inconclusive for noninferiority
 - No difference between groups for noninferiority
 - Non-inferior
 - Superior
27. The following results were found in a 2-year noninferiority trial that compared a new anticoagulant with warfarin for stroke prevention in atrial fibrillation: warfarin 8%, new anticoagulant 8.8%; HR 1.10 (95% CI, 0.90–1.30). The noninferiority margin set by the authors was a HR of 1.46. Which one of the following would best help the clinician assess these results?
- Calculate NNT
 - Calculate NNH
 - Need more information to calculate NNT/NNH
 - Not advisable to calculate NNT/NNH
28. A case-control study examined the association between use of acetaminophen and an elevated INR in a population of patients taking warfarin. Which one of the following would be most concerning for high risk of bias from this type of study?
- Patients were exposed to acetaminophen before determining INR value.
 - Patients were contacted to determine their amount of acetaminophen exposure by interviewers who were aware of the outcome status (INR results).
 - Multivariable analysis was conducted to adjust for differences in baseline characteristics.
 - There was a dose-response gradient between increasing exposure to acetaminophen dose and the outcome status (an elevated INR).

29. Which of the following statements best describes the design of a case-control study?
- The groups are defined by their exposure status.
 - The groups are defined by the outcome status.
 - The groups are not defined in advance.
 - The cases serve as their own control.
30. A group of investigators is comparing the risk of myocardial infarction with NSAIDs versus no NSAIDs in a retrospective cohort study. There are baseline differences in patient characteristics prognostic for myocardial infarction. Which of the following measures, if present, would best reduce this potential risk of bias?
- Authors state that the exposure preceded the outcome.
 - There was a dose response gradient investigated.
 - Multivariable logistic regression was employed.
 - Myocardial infarction was measured similarly in both groups.
31. A case-control study found that antibiotic exposure was significantly higher in warfarin users who developed bleeding versus those who did not develop bleeding. In reading the results section, which one of the following would present these results in the most valid way?
- ARR 2% (1%–4%)
 - OR 1.73 (1.49–2.10)
 - HR 1.85 (1.22–3.56)
 - RR 0.85 (0.73–0.99)
32. Which of the following statements from the methods section of a study best describes propensity score methods?
- We conducted a multivariable Cox proportional hazards model that adjusted for individual covariates that differed significantly at baseline.
 - The primary noninferiority hypothesis required that apixaban preserve at least 50% of the relative reduction in stroke risk compared with warfarin.
 - The standardized differences of covariates for matched patients demonstrated adequate balance with no standardized differences > 0.1.
 - Each person served as his or her own control and thereby eliminated confounding due to all fixed characteristics.
33. A propensity score-adjusted cohort study design is most similar to which of the following study designs?
- Nested case-control study
 - Propensity score-matched study
 - Traditional retrospective cohort study
 - Randomized, controlled noninferiority trial
34. You are reading a propensity score-matched study examining the association of digoxin with mortality in patients with atrial fibrillation. Which proportion of digoxin-treated patients matched to a control patient would best indicate generalizability of the study results?
- 0%
 - 20%
 - <0.05
 - 80%
35. Which of the following study designs would best allow investigators to report event rates and absolute differences directly, without further adjustments?
- Case-control study
 - Propensity score-adjusted cohort study
 - Propensity score-matched cohort study
 - Nested case-control study
36. A group of investigators is considering using a case-crossover design to evaluate the safety of spironolactone in patients with heart failure. Which of the following outcomes would be most appropriate for the investigators to evaluate considering this study design and the outcome of interest?
- Heart failure-related death
 - Arrhythmic death
 - Need for ICD
 - Hyperkalemia
37. You are reading an instrumental variable analysis study that compares the type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients. The study uses the hospital's preferred prophylaxis agent as an instrumental variable. Which one of the following type of instruments does this best represent?
- Distance to facility
 - Regional variation
 - Facility variation
 - Physician variation
38. You are reading an instrumental variable analysis study that compares the type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgery patients. The study uses the hospital's preferred stress ulcer prophylaxis agent as an instrumental variable. You see in the baseline characteristics table that a proton pump inhibitor is the agent more commonly preferred in rural hospitals. Which one of the following best describes this difference in baseline characteristics?
- Potential instrument-outcome confounder
 - Instrumental variable
 - Potential marginal patient confounder
 - Distance to facility instrument
39. You are reading an instrumental variable analysis study that compares the type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgery

patients. The study uses the hospital's preferred prophylaxis agent as an instrumental variable. In the instrumental variable analysis, use of the proton pump inhibitor (compared with an H2 receptor antagonist) was associated with an absolute risk of pneumonia of 8.5 cases per 1000 patients (95% CI, 0.5–15.9). Which one of the following best interprets these results?

- A. There is no significant difference in the risk of pneumonia between groups.
 - B. There is a significantly increased risk of pneumonia with PPI compared with an H2 blocker
 - C. There is a significantly decreased risk of pneumonia with PPI compared with an H2 blocker
 - D. It is not appropriate to compare risk of pneumonia using an instrumental variable analysis
40. Assuming that best methods possible are used, which one of the following study designs has the lowest risk of bias?
- A. Case-control study
 - B. Nested case-control study
 - C. Propensity score-matched study
 - D. Propensity score-adjusted study

Learner Chapter Evaluation: Beyond Randomized Placebo Controlled Trials in Cardiology.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

21. The content of the chapter met my educational needs.
22. The content of the chapter satisfied my expectations.
23. The author presented the chapter content effectively.
24. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
25. The content of the chapter was objective and balanced.
26. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
27. The content of the chapter was useful to me.
28. The teaching and learning methods used in the chapter were effective.
29. The active learning methods used in the chapter were effective.
30. The learning assessment activities used in the chapter were effective.
31. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

32. Judge the utility of evidence from non-randomized placebo controlled trial clinical study designs to answer clinical questions.
33. Evaluate the validity and applicability of active control superiority trial data to patient care.
34. Evaluate the validity and applicability of noninferiority trial data to patient care.
35. Distinguish between types of traditional observational study designs.

36. Evaluate the validity and applicability of evidence from traditional observational study designs to patient care.
37. Distinguish between types of novel observational study designs.
38. Evaluate the validity and applicability of evidence from novel observational study designs to patient care.
39. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
40. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 41–43 apply to the entire learning module.

41. How long did it take you to read the instructional materials in this module?
42. How long did it take you to read and answer the assessment questions in this module?
43. Please provide any additional comments you may have regarding this module:

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<i>Infection Critical Care</i>	January 15, 2016	May 16, 2016	January 14, 2019
<i>Medication Administration /Critical Care Research</i>	May 16, 2016	September 15, 2016	May 14, 2019
<i>Pain and Sedation/ Support and Prevention</i>	September 15, 2016	January 17, 2017	September 14, 2019
<i>Cardiology Critical Care</i>	January 17, 2017	May 15, 2017	January 14, 2020
<i>Renal/ Pulmonary Critical Care</i>	May 15, 2017	September 15, 2017	May 14, 2020
<i>Neurocritical Care/ ICU Technology</i>	September 15, 2017	January 16, 2018	September 14, 2020
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