



# Hypertensive Emergencies

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## LEARNING OBJECTIVES

1. Evaluate the hemodynamic disturbances in hypertensive crisis and classify its presentation.
2. Evaluate the therapeutic goals for general hypertensive emergency and exceptions to the general principles (compelling conditions).
3. Assess the potential of using blood pressure variability as a therapeutic goal and monitoring value.
4. Design optimal pharmacotherapy for the patient with hypertensive emergency.

### ABBREVIATIONS IN THIS CHAPTER

BPV	Blood pressure variability
CCB	Calcium channel blocker
CPP	Cerebral perfusion pressure
HELLP	Hemolysis, elevated liver enzymes, low platelet count
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
MAP	Mean arterial pressure
PD	Pharmacodynamics
PK	Pharmacokinetics

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

## INTRODUCTION

Hypertensive crises are acute, severe elevations in blood pressure that may or may not be associated with target-organ dysfunction. Hypertensive emergencies, a subset of hypertensive crises, are characterized by acute, severe elevations in blood pressure, often greater than 180/110 mm Hg (typically with systolic blood pressure [SBP] greater than 200 mm Hg and/or diastolic blood pressure [DBP] greater than 120 mm Hg) associated with the presence or imminence of target-organ dysfunction (Muesan 2015; Mancia 2013; Johnson 2012; Chobanian 2003). Hypertensive urgencies are characterized by a similar acute elevation in blood pressure but are not associated with target-organ dysfunction. Table 1-1 lists example conditions that, when accompanied by high blood pressure, define hypertensive emergency.

Although hypertensive emergencies can lead to significant morbidity and potentially fatal target-organ damage, only 1%–3% of patients with hypertension will have a hypertensive emergency during their lifetime (Deshmukh 2011). Within the hypertensive crises, hypertensive emergencies account for only around one-fourth of presentations compared with hypertensive urgencies, which account for around three-fourths (Zampaglione 1996). Despite the low incidence of hypertensive emergencies, hospitalizations because of hypertensive emergencies have increased since 2000 (Deshmukh 2011), possibly because of the heightened awareness, recognition, and subsequent diagnosis of hypertensive emergency. However, even though more hospitalizations are secondary to hypertensive emergencies, mortality remains low, with an in-hospital mortality of around 2.5% and 1- and 10-year survival greater than 90% and 70%, respectively (Deshmukh 2011; Lane 2009; Webster 1993).

Many risk factors and causes are associated with the development of hypertensive crises. In a small longitudinal analysis from Switzerland, hypertensive crises were more often associated with

female sex, higher grades of obesity, presence of hypertensive or coronary heart disease, presence of mental illness, and higher number of antihypertensive medications, with the strongest association related to patient nonadherence to antihypertensive medications (Saguner 2010). Causes vary nationally, regionally, and institutionally, but common causes include intoxications (e.g., cocaine, amphetamines, phencyclidine hydrochloride, stimulant diet supplements), nonadherence to antihypertensive regimens, withdrawal syndromes (e.g., clonidine or  $\beta$ -antagonists), drug-drug/drug-food interactions (e.g., monoamine oxidase inhibitors and tricyclic antidepressants, antihistamines, or tyramine), spinal cord disorders, pheochromocytoma, pregnancy, and collagen vascular disease (e.g., systemic lupus erythematosus) (Johnson 2012; Aggarwal 2006; Shea 1992).

Recent investigations into the pathophysiology of hypertensive crises have failed to clarify the exact mechanisms involved. Autoregulatory changes in vascular resistance

through the autocrine/paracrine system occur in response to the production of endogenous vasoconstrictors (e.g., catecholamines) or endogenous vasodilators (e.g., nitric oxide) (Parrillo 2008). During a hypertensive emergency, acute elevation in blood pressure overwhelms the autoregulation of the endothelial control of vascular tone, leading to mechanical vascular wall stress with subsequent endothelial damage and vascular permeability (Vaughan 2000). This permeability leads to the leakage of plasma into the vascular wall, resulting in activation of platelets, initiation of the coagulation cascade, deposition of fibrin, and recruitment of inflammatory mediators (Derhaschnig 2013; Shantsila 2011; van den Born 2011). This inappropriate vasoconstriction and microvascular thrombosis leads to hypoperfusion and end-organ ischemia with subsequent target-organ dysfunction.

Although any target organ can be affected by acute, severe, uncontrolled hypertension in theory, analyses show that some organs are more commonly affected than others (see Table 1-1) (Zampaglione 1996). Differences in the amount of cardiac output received, total oxygen consumption, and autoregulatory capacity (i.e., autoregulatory dependence) may explain some of the differences in the prevalence of individual organ dysfunction (Myers 1948).

In patients with acute, severe elevations in their blood pressure, thorough laboratory and diagnostic evaluations are warranted. Often, the specific tests ordered and evaluated are guided by the presenting symptomatology and will vary depending on individual presentation. These tests can include blood pressure measurement in both arms, urine toxicology screen, funduscopic examination, serum glucose, creatinine, electrolytes, CBC, liver function tests, urinalysis (in search of proteinuria and hematuria), chest radiography, ECG, echocardiography, urine or serum pregnancy screening, and head or chest CT (Muesan 2015).

## BASELINE KNOWLEDGE STATEMENTS

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

- Knowledge of hemodynamic relationships and interactions – specifically, the impact of preload, afterload, heart rate, and cardiac output on mean arterial pressure
- Familiarity with clinical symptomatology and routine laboratory and diagnostic data that support or refute the presence/absence of target-organ damage

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

## ADDITIONAL READINGS

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

- [JNC 7 Complete Report: The Science Behind the New Guidelines](#)
- Whelton PK, Carey RM, Aronow SW, et al. [2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults](#). J Am Coll Cardiol 2017.
- Rhoney D, Peacock WF. [Intravenous therapy for hypertensive emergencies, part 1](#). Am J Health Syst Pharm 2009;66:1343-52.
- Rhoney D, Peacock WF. [Intravenous therapy for hypertensive emergencies, part 2](#). Am J Health Syst Pharm 2009;66:1448-57.
- Parati G, Ochoa JE, Lombardi C, et al. [Assessment and management of blood pressure variability](#). Nat Rev Cardiol 2013;10:143-55.

## TREATMENT GOALS

Treatment goals for hypertensive crises depend on classification (e.g., emergency vs. urgency) and presenting condition. Many presenting conditions have unique treatment goals, including time to goal, additional treatment parameters, and treatment modalities, to achieve set goals. These conditions are considered exceptions to the general treatment principles of hypertensive crisis and in most recent guidelines termed “compelling conditions” (Whelton 2017). For the general treatment of hypertensive crisis, patients should be classified as having hypertensive emergency or hypertensive urgency. Hypertensive urgency often requires initiating, reinitiating, modifying, or titrating oral therapy and usually does not require ICU or hospital admission (Muesan 2015). The treatment target for hypertensive urgency is a gradual blood pressure reduction over 24–48 hours to the goals as laid out in the most recent rendition of hypertension management guidelines on the basis of compelling indications (James 2014; Muesan 2015; Whelton 2017). The more common error

**Table 1-1.** Examples of Acute Target-Organ Damage and Clinical Manifestations of Hypertensive Emergency

End-Organ System	Prevalence (%)
<b>Neurologic</b>	
Cerebral infarction	24.5
Hypertensive encephalopathy	16.3
ICH or SAH	4.5
<b>Cardiovascular</b>	
Acute pulmonary edema (left ventricular failure)	22.5
Acute congestive failure (left and/or right ventricular failure)	14.3
Acute coronary ischemia (myocardial infarction or unstable angina)	12
<b>Renal</b>	
Acute kidney injury/failure	< 10
<b>Liver</b>	
Liver enzyme elevation (most commonly associated with HELLP syndrome)	0.1–0.8
<b>Ocular</b>	
Retinal hemorrhage/exudate	0.01–0.02
<b>Vascular</b>	
Eclampsia	4.5
Aortic dissection (type A or B)	2

HELLP = hemolysis, elevated liver enzymes, low platelet count; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage.

Information from: Shantsila A, Dwivedi G, Shantsila E, et al. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension* 2011;57:490-6; Vidaeff AC, Carroll MA, Ramin SM. Acute hypertensive emergencies in pregnancy. *Crit Care Med* 2005;33:S307-12; and Zampaglione B, Pascale C, Marchisio M, et al. Hypertensive urgencies and emergencies. Prevalence and clinical presentation. *Hypertension* 1996;27:144-7.

with the treatment of hypertensive urgency is overaggressive correction because no benefit, but potential harm, may be associated with too rapid a decrease in blood pressure (Bertel 1987; Reed 1986; Bannan 1980). Avoiding overaggressive correction is particularly important in patients with chronic hypertension because their end organs adapt to chronically elevated blood pressures, setting a new physiologic “norm” of autoregulation (Serrador 2001). This new “norm” leads to optimal organ perfusion at a higher baseline blood pressure. If this autoregulatory shift is unrecognized during a hypertensive emergency, patients may be at risk of harm from overcorrection or over-normalization of blood pressure.

In the treatment of hypertensive emergency, patients who would fall into the general treatment goals should be identified, as should those who would have exceptions to the

general treatment goals (compelling conditions). For patients without exceptions, the goal of therapy is to reduce the mean arterial pressure (MAP) by 25% over the first hour of therapy (Table 1-2) (Muesan 2015; Mancia 2013; Chobanian 2003). Greater reductions (by more than 25%) have been associated with the induction of cerebral ischemia (Bertel 1987; Reed 1986; Strandgaard 1984; Bannan 1980). In addition, if neurologic deterioration is noted during the initial 25% MAP reduction (or during subsequent lowering), therapy should be discontinued (Calhoun 1990). After the first hour, a more gradual blood pressure reduction is recommended (Muesan 2015; Mancia 2013; Chobanian 2003).

For individual populations that qualify for exceptions to the general treatment goals (compelling conditions), see the text below. These populations include patients with aortic

**Table 1-2.** BP Treatment Goals for Hypertensive Emergency

Goal Time <sup>a</sup>	BP Target
First hour	Reduce MAP by 25% (while maintaining goal DBP $\geq$ 100 mm Hg)
Hours 2–6	SBP 160 mm Hg and/or DBP 100–110 mm Hg
Hours 6–24	Maintain goal for hours 2–6 during first 24 hr
24–48 hr	Outpatient BP goals according to the 2017 Guidelines for Management of High Blood Pressure in Adults

<sup>a</sup>See exceptions to these goals for conditions that qualify.

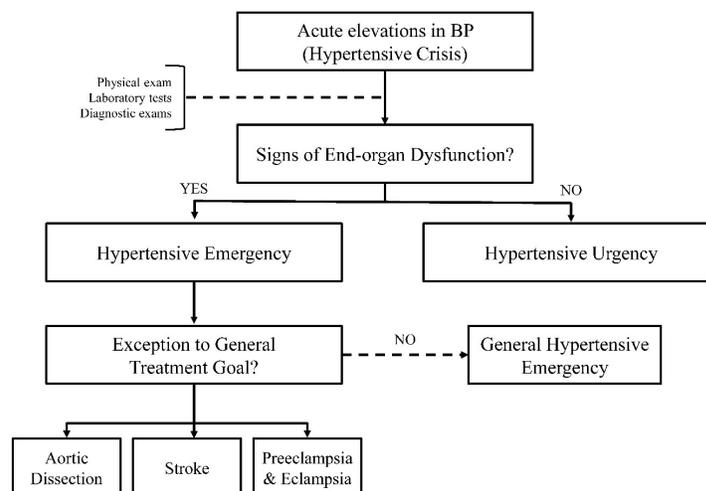
BP = blood pressure; JNC = Joint National Committee.

dissection, acute stroke (ischemic and hemorrhagic), and pregnancy-associated severe hypertension (preeclampsia/eclampsia and hypertensive emergency in the pregnant patient) (Figure 1-1). Each of these populations has unique treatment targets, considerations for subpopulations within them, or additional considerations during treatment.

### Acute Aortic Dissection

Aortic dissections can be classified on the basis of anatomic location and involvement of the aorta. The Stanford classification system classifies aortic dissections into the ascending aorta with or without distal aorta involvement (type A) and those involving only the aortic arch or descending aorta (type B). In general, type A or life-threatening type B (i.e., malperfusion syndrome, rapidly progressing dissection, enlarging

aneurysm, or inability to control blood pressure or symptoms with medications) aortic dissections are surgical emergencies (Hiratzka 2010). Medical management should be considered first line for most non-life-threatening type B aortic dissections. Because propagation of the aortic dissection is related to shear stress (a principle related to blood flow velocity and rate), the treatment goal for aortic dissection is 2-fold: blood pressure and heart rate control (Hiratzka 2010; Papaioannou 2005). The goal heart rate during acute management of aortic dissection is less than 60 beats/minute within minutes of presentation, if possible. In addition, the goal blood pressure after achieving adequate heart rate control is SBP less than 120 mm Hg and/or as low as clinically tolerated (i.e., lowest blood pressure that maintains end-organ perfusion).



**Figure 1-1.** Treatment goal decision-algorithm in hypertensive crisis.

BP = blood pressure.

### **Acute Ischemic Stroke**

Hypertension associated with ischemic stroke is often considered an adaptive response to maintain cerebral perfusion pressure (CPP) to the brain, which is equal to the difference between MAP and intracranial pressure (ICP) [CPP = MAP - ICP]. Because ischemic strokes can be associated with increases in ICP, acute treatment of MAP elevations is only indicated in limited circumstances. Currently, the guidelines recommend acute treatment in three instances: (1) use of thrombolytic therapy, (2) other target-organ damage (e.g., aortic dissection, myocardial infarction), or (3) "severe" elevations in blood pressure (SBP greater than 220 mm Hg and/or DBP greater than 120 mm Hg) (Jauch 2013). If thrombolytic therapy is warranted, the blood pressure goal before initiating thrombolysis is less than 185/110 mm Hg. After commencement and throughout thrombolysis, and for the subsequent 24 hours, that goal changes slightly to a goal blood pressure less than 180/105 mm Hg. This blood pressure control has been associated with fewer intracerebral hemorrhages (ICHs) associated with intravenous thrombolysis (Ahmed 2009). In the other ischemic stroke circumstances (other target-organ damage or severe elevations) requiring treatment of elevated blood pressure, the goal is a more modest reduction of 15% (10%–20%) in the MAP over 24 hours, allowing for maintenance of CPP while theoretically avoiding the complications of cerebral edema exacerbation and hemorrhagic transformation (Figueroa 2015; Johnson 2012; Hiratzka 2010, Whelton 2017).

### **Acute Hemorrhagic Stroke**

Similar to ischemic stroke, acute hemorrhagic strokes can increase ICP, potentially compromising CPP. Because of this risk, acute hypertension in this setting may again be adaptive (Strandgaard 1976; Symon 1973; Lassen 1959). Recent evidence shows that blood pressure elevations during acute ICHs are associated with hematoma expansion, neurologic deterioration, inability to perform activities of daily living, and death (Rodriguez-Luna 2013; Weiss 2008). Investigations have begun evaluating rapid blood pressure reductions in the acute ICH population. In hyperacute (less than 3 hours) and acute (less than 4.5 hours) treatment of patients with ICH without ICP elevations, a target SBP goal of less than 160 mm Hg over the first few hours is relatively safe and may confer benefit regarding functional recovery, if achieved (Wang 2015; Anderson 2013; Sakamoto 2013; Arima 2012; Arima 2010). However, although the guidelines support this blood pressure target in this patient subgroup with ICH, the degree of blood pressure reduction must be noted. In the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial, patients were randomized to either an SBP target of less than 140 mm Hg or a target of 140–180 mm Hg acutely after their ICH hypertensive emergency (Qureshi 2016). Functional outcomes did not differ, and the incidence of renal adverse events was significantly higher (9% vs. 4%, respectively;  $p=0.002$ ) if

patients were randomized to the aggressive blood pressure target. Because the average SBP on study entry was 200.6 mm Hg ( $\pm 27$  mm Hg), the lack of outcome benefit and the increased incidence of renal adverse events may have been caused by the large relative reduction in SBP (around 60 mm Hg) in the aggressive treatment arm. This was a higher relative blood pressure reduction than in other, similar studies. In addition, in patients with "severe" elevations in blood pressure (e.g., SBP greater than 220 mm Hg), patients with large hematomas, or those with known elevations in ICP, it is unclear whether aggressive treatment targets are safe because these patients were excluded from all recent studies on aggressive, rapid blood pressure lowering. In this patient subgroup with ICH (those excluded from recent studies), the guidelines recommend a more modest reduction to SBP less than 180 mm Hg or MAP less than 130 mm Hg over the first 24 hours (Hemphill 2015). Of interest, what may be more consistently associated with benefit in the patient group with acute ICH is a decreased variability in blood pressure during the presentation and treatment of acute ICH. More information will be discussed in the Blood Pressure Variability section.

### **Preeclampsia/Eclampsia and Hypertensive Emergency in Pregnancy**

Hypertensive disorders are common during pregnancy and can be classified into four pregnancy-associated categories: (1) chronic hypertension, (2) gestational hypertension, (3) preeclampsia, and (4) chronic hypertension with superimposed preeclampsia (ACOG 2013). In addition, non-pregnancy-associated hypertensive emergencies can occur in the pregnant patient (Sibai 2014). In general, because of the maternal (e.g., acute renal failure, placental abruption, cerebrovascular accident, myocardial infarctions, respiratory distress) and fetal (e.g., preterm birth, low birth weight, fetal demise) risks associated with hypertensive emergencies and preeclampsia/eclampsia (either in isolation or superimposed), these disorders are treated with medical urgency (Orbach 2013; Kuklina 2009; Vidaeff 2005). One of the main differences in this population is the terminology and criteria surrounding acute hypertension in the pregnant patient (Table 1-3).

Compared with other populations, pregnant patients with acute hypertension are considered to have "severe" hypertension if their SBP is 160 mm Hg or greater or their DBP is 110 mm Hg or greater (ACOG 2013). Preeclampsia, by definition, is an elevation in blood pressure (SBP of 140 mm Hg or greater or DBP of 90 mm Hg or greater on two occasions 4 hours or more apart) after 20 weeks' gestation with either proteinuria or other "severe features" (see Table 1-3). Other dangerous forms of acute high blood pressure include eclampsia (presence of new-onset grand mal seizures in a woman with preeclampsia) and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) (see Table 1-3). Of note, however, HELLP syndrome is not universally associated with elevated blood pressure (Sibai 2014). Persistent blood pressure readings

**Table 1-3.** Acute Hypertensive Definitions in the Pregnant Patient

Name	BP Criteria	Additional Criteria
“Severe” acute hypertension	SBP $\geq$ 160 mm Hg or DBP $\geq$ 110 mm Hg	-
Preeclampsia	SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg	BP readings must occur on $\geq$ 2 occasions, $\geq$ 4 hr apart > 20 weeks gestation Either: <ul style="list-style-type: none"> <li>Proteinuria (24 hr urine collection <math>\geq</math> 300 mg protein OR spot urine collection Uprotein/UCr <math>\geq</math> 0.3 mg/dL)</li> <li>Severe features<sup>a</sup></li> </ul>
Eclampsia	Preeclampsia degree of BP elevation	New-onset grand mal seizures in a woman with no known seizure disorder
HELLP syndrome	With or without preeclampsia degree of BP elevation	Evidence of the following: <ul style="list-style-type: none"> <li>Hemolysis (schistocytes on peripheral smear, increased LDH, decreased haptoglobin, increased Tbili [<math>\geq</math> 1.2 mg/dL], decreased Hct)</li> <li>Elevated liver enzymes (AST/ALT (<math>\geq</math> 70 IU/L))</li> <li>Low Plt (&lt; 100,000 mcL)</li> </ul>
Hypertensive emergency	BP $\geq$ 240/140 mm Hg	-

<sup>a</sup>Severe features = SBP  $\geq$  160 mm Hg or DBP  $\geq$  110 mm Hg, Plt < 100,000/mm<sup>3</sup>, AST/ALT > 2 x ULN, right upper quadrant or epigastric pain unresponsive to medication, cerebral/visual symptoms, renal injury (SCr > 1.1 mg/dL or > 2 x baseline), or pulmonary edema. Tbili = total bilirubin; UCr = urinary creatinine; ULN = upper limit of normal; Uprotein = urinary protein.

greater than 240/140 mm Hg often indicate a hypertensive emergency in the pregnant population (Vidaeff 2005).

In addition to the different terminology defining acute hypertension in pregnancy, treatment goals differ compared with general hypertensive crises. In preeclampsia, blood pressure elevations are considered the only modifiable target of therapy similar to that of hypertensive emergency (CMACE 2011). The blood pressure target goal for hypertensive emergency and preeclampsia is less than or equal to 160/110 mm Hg with attention paid to avoid abrupt decreases in blood pressure which can lead to potential harmful fetal effects (Vidaeff 2005). Because of this caution, the MAP should be decreased by 20%–25% over the first few minutes to hours and blood pressure further decreased to the target of 160/110 mm Hg or less over the subsequent hours (ACOG 2013; Vidaeff 2005).

## BLOOD PRESSURE VARIABILITY

An emerging therapeutic consideration for the treatment of hypertensive emergency is the concept of blood pressure variability (BPV). By definition, BPV is a standardized way of representing changes in blood pressure over time (Parati 2013). Intrinsicly, differences (variability) exist in the pressure present in the arterial circulatory system during the

cardiac cycle, as evidenced by the inherent differences in SBP and DBP (Mancia 1986). In addition, beat-to-beat, diurnal, and physiologic variations occur in the SBP and DBP because of the interplay of humoral, behavioral, and environmental factors (Schillaci 2012; Mancia 2000; Mancia 1986; Conway 1984). All of these can lead to differences in BPV. Blood pressure variability can be expressed several different ways. Table 1-4 lists common calculations for BPV indexes.

In the ambulatory setting, lower mid- and long-term within-individual visit-to-visit BPVs, in addition to absolute average blood pressure lowering, may be associated with cardiovascular protection, including protection from stroke, myocardial infarction, and both cardiovascular and all-cause mortality (Hashimoto 2012; Johansson 2012; Rothwell 2010). In addition, BPV profiles between medication classes differ significantly (Ishikura 2012; Rothwell 2010). Given this information, investigation has turned to the acute care setting with exploration into subpopulations of hypertensive emergency.

During the acute phase of stroke, blood pressure regulation is impaired, leading to blood pressure elevation and lability (Sykora 2008). The exact mechanism for this finding is currently unknown, but it is thought to be related to impairment in the baroreflex (Henderson 2004). The baroreflex is responsible for detecting changes in blood pressure in the

**Table 1-4.** Blood Pressure Variability Indexes

Index Variable <sup>a</sup>	Description
Standard deviation (SD)	Computed as the square root of the mean of the squares of the deviations from the arithmetic mean over the sample period (e.g., 24 hr)
Coefficient of variation (CoV)	Computed as the SD divided by the mean
Average real variability (ARV)	Computed as the average of the absolute differences between consecutive BP measurements over time (e.g., 24 hr)
Residual BPV	Computed in the frequency domain through spectral analysis of BP fluctuations over time (e.g., 24 hr)
Weighted 24-hr SD	Computed by weighting the average of daytime and nighttime BP SD for the duration of the day and nighttime periods and by averaging the SD of these two sub-periods

<sup>a</sup>Can be calculated for SBP, DBP, or MAP.

Information from: Parati G, Ochoa JE, Lombardi C, et al. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep* 2015;17:537.

carotids, cardiac chambers, and aortic arch and responding by adjusting the heart rate through vagal innervation or changing the peripheral vascular tone through sympathetic innervation. During acute stroke, there may be some degree of baroreceptor failure in the impairment of the baroreception, central processing of this detection, or sensitivity of the response from the baroreceptors – known as baroreflex sensitivity (BRS) (Sykora 2008; Phillips 2000; Robinson 1997). Of importance, in the acute ICH population, decreased BRS and increased beat-to-beat BPV are strongly correlated (Sykora 2008).

Given the prognostic significance of BPV in the ambulatory setting and the known increased BPV in the acute ICH population, it is intuitive to investigate the impact of BPV on clinical outcomes in this population. Post hoc analyses of clinical investigations have shown a correlation between decreased BPV and improved early neurologic function (Rodriguez-Luna 2013), favorable neurologic recovery (Tanaka 2014), and decreased incidence of death or major disability (Manning 2014). Each of these analyses showed that despite the degree of actual blood pressure control, patients who had more BPV fared worse. However, many questions remain, despite these positive findings. These include: How do we measure BPV at the bedside in real-time? Which measure of BPV correlates best with outcomes and do the various measures of BPV correlate with one another? Are these findings consistent in other populations with hypertensive emergency? What is the exact therapeutic target and timing of decreasing BPV? How does medication selection affect BPV?

Although answers to these questions largely remain unknown, limited information is available comparing medication regimens in the acute care setting. In the acute ICH population, both retrospective and prospective

investigations of nicardipine have shown superior performance regarding BPV compared with labetalol (SD-SBP: 8.19 mm Hg vs. 10.78 mm Hg;  $p=0.003$ ; 15 mm Hg vs. 19 mm Hg;  $p<0.001$ , respectively), but no clinical significance in those analyses was shown (Liu-DeRyke 2013; Liu-DeRyke 2008). In addition, in treating perioperative hypertension in the cardiac surgery population, clevidipine had significantly better BPV than did nitroglycerin and sodium nitroprusside ( $p=0.0004$ ) and numerically better BPV than nicardipine, and decreased BPV was positively correlated with the clinical outcomes of decreased time to extubation (7.1 hours vs. 7.5 hours;  $p=0.05$ ) and decreased postoperative length of stay (122.4 hours vs. 141.6 hours;  $p<0.0001$ ) (Aronson 2014; Aronson 2008). Furthermore, in hypertensive emergencies associated with symptoms of acute heart failure, clevidipine compared with the standard of care (largely nitroglycerin and nicardipine) showed significantly better initial monotherapy achievement of target blood pressure (71% vs. 37%;  $p=0.002$ ) without the need for additional agents (16% vs. 51%;  $p=0.0005$ ), perhaps indirectly indicating a better BPV profile (Peacock 2014). Together with these findings was also the improvement in clinical symptomatology with the demonstration of a faster resolution of self-reported dyspnea.

Although these results regarding BPV are promising, additional exploratory and confirmatory studies are needed to answer the additional questions surrounding its application to the treatment of hypertensive emergency. Specifically, the impact of BPV in other hypertensive emergency populations and the specific BPV index that should be targeted are unknown. Although additional investigation is underway, use of BPV as a primary therapeutic target at this point would be considered investigational.

## Patient Care Scenario

A 52-year-old man with a medical history of hypertension, sarcoidosis, and asthma presents to the ED with new severe, sharp headache. He states that it started about 3 hours ago and is getting worse.

The patient's vital signs include blood pressure 192/102 mm Hg, heart rate 78 beats/minute, respiratory rate 20 breaths/minute, and pain 9/10, while afebrile.

### ANSWER

First, determine whether the patient has signs or symptoms of target-organ damage. In general, the patient's physical examination and presenting symptoms will lead toward which diagnostic tests and laboratory assays to use. Laboratory values do not indicate specific target-organ damage. Diagnostic head CT evaluation reveals target-organ damage to the brain, specifically the development of an ICH. Because of this finding, the patient qualifies for a hypertensive emergency warranting intravenous therapy and ICU admission. Second, determine whether the patient is an exception to the general treatment principles of hypertensive emergency. Patients with these exceptions include those with aortic dissection; pregnancy-associated acute,

Laboratory test results show SCr 0.8 mg/dL (baseline 0.7 mg/dL), AST 32 U/L, total bilirubin 0.7 mg/dL, and lipase 40 units/L. A head CT reveals a small acute ICH with no mass effect or edema.

Classify this patient's hypertensive crisis and decide on the appropriate treatment goals.

severe hypertension; and acute strokes. With his acute ICH, this patient would qualify as an exception to the general treatment principles for hypertensive emergency. In addition, with ICH, further delineation is required. Although rapid, aggressive blood pressure lowering has been shown to be safe, these large studies excluded patients with large ICH volumes, ICP elevations, and/or severe elevations in blood pressure (SBP greater than 220 mm Hg). Because G.A. does not meet any of these exclusion criteria, the blood pressure goal would be SBP less than 160 mm Hg within the first few hours, being mindful of overaggressive correction. In addition, he would likely benefit from minimal BPV, and an agent with an optimal BPV profile would be best.

1. Johnson W, Nguyen ML, Patel R. Hypertension crisis in the ED. *Cardiol Clin* 2012;30:533-43.

2. Hemphill JC III, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46:2032-60.

3. Manning L, Hirakawa Y, Arima H, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurol* 2014;13:364-73.

## TREATMENT OF HYPERTENSIVE EMERGENCY

Given the diverse presentations of hypertensive emergency, it is challenging to label one medication as the drug of choice. In fact, systematic review has failed to show the superiority of any medication or medication class to another regarding clinical outcomes of hypertensive emergency (Perez 2008). Choice of medication often depends on a risk-benefit analysis of each agent considering the (1) affected target organ on presentation, (2) pharmacokinetics (PK) and pharmacodynamics (PD) of the medications available, and (3) hemodynamic, adverse effect, and BPV profile of the medication options. Preferable traits of medications used to treat hypertensive emergencies include intravenous administration, ability to be titrated to desired effect allowing for a "smooth" reduction of blood pressure, short duration of activity, and minimal adverse effect profile. Extreme caution should be used with acute and profound lowering of blood pressure, given that over-normalization has led to the induction of ischemic complications (Strandgaard 1984). Investigations have shown that 10%–66% of patients may have over-normalization of blood pressure during their treatment of hypertensive emergency, demonstrating the challenge of this goal of smooth, target-associated blood pressure reduction (Grise 2012; Vuylsteke 2011).

Table 1-5 includes the medications available for the treatment of hypertensive emergency as well as the PK, PD, and hemodynamic effects of each agent. When selecting an agent, these parameters must be considered.

## MEDICATIONS USED IN HYPERTENSIVE EMERGENCY

Sodium nitroprusside is a potent arterial and venous vasodilator that has been used extensively in the treatment of hypertensive emergency because of its favorable PK parameters (see Table 1-5). Sodium nitroprusside is a nitric oxide donor, leading to smooth muscle relaxation (Rhoney 2009). Because it works directly at smooth muscle, sodium nitroprusside reduces both afterload and preload, giving it wide applicability for various hypertensive emergencies. Two PD effects of concern with sodium nitroprusside are "coronary steal" and increases in ICP. Coronary steal is the concept of redistributing oxygenated blood from diseased coronary arteries toward non-diseased coronary arteries because non-diseased coronary arteries can preferentially vasodilate. In theory, this would then shunt oxygenated blood away from ischemic areas. Sodium nitroprusside may result in this preferential vasodilation, leading to reduced coronary perfusion pressure (Mann 1978), and thus should be avoided in patients presenting with myocardial infarction as their

**Table 1-5.** Medications Used in Hypertensive Emergencies

Agent	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
<b>Vasodilators</b>						
Hydralazine	IV bolus: 10–20 mg IM: 10–40 mg q30min PRN	IV: 10 min IM: 20 min	IV: 1–4 hr IM: 2–6 hr	↔	↓	↑
Nitroglycerin	IV 5–200 mcg/min Titrate by 5–25 mcg/min q5–10min	2–5 min	5–10 min	↓↓	↓↔	↔↑
Sodium nitroprusside	IV 0.25–10 mcg/kg/min Titrate by 0.1–0.2 mcg/kg/min q5min	Seconds	1–2 min	↓	↓↓	↑
<b>Calcium Channel Blockers</b>						
Clevidipine	IV 1–6 mg/hr Titrate by 1–2 mg/hr q90s; max 32 mg/hr <sup>a,b</sup>	1–4 min	5–15 min	↔	↓	↑
Nicardipine	IV 5–15 mg/hr Titrate by 2.5 mg/hr q5–10min <sup>c</sup>	5–10 min	2–6 hr	↔	↓	↑
<b>β-Blockers</b>						
Esmolol	IV 25–300 mcg/kg/min (bolus of 500 mcg/kg not often required, given short onset) Titrate by 25 mcg/kg/min q3–5min	1–2 min	10–20 min	↔	↔	↓
Labetalol	IV bolus: 20 mg; may repeat escalating doses of 20–80 mg q5–10min PRN IV 0.5–10 mg/min Titrate by 1–2 mg/min q2hr, given the agent's longer half-life, and consider dose reduction after BP control is achieved	2–5 min, peak 5–15 min	2–6 hr Up to 18 hr	↔	↓	↓
Metoprolol	IV bolus: 5–15 mg q5–15min PRN	5–20 min	2–6 hr	↔	↔	↓
<b>ACEI</b>						
Enalaprilat	IV bolus: 1.25 mg q6hr Titrate no more than q12–24hr; max dose: 5 mg q6hr	15–30 min	12–24 hr	↓	↓	↑
<b>α-Antagonist</b>						
Phentolamine	IV bolus: 1–5 mg PRN; max 15 mg	Seconds	15 min	↔	↓	↑
<b>D<sub>1</sub> Receptor Agonists</b>						
Fenoldopam	IV 0.03–1.6 mcg/kg/min Titrate by 0.05–1 mcg/kg/min q15min	10–15 min	10–15 min	↔↓	↓	↑

<sup>a</sup>Limited data for extended use of 32 mg/hr.

<sup>b</sup>24-hr max dose = 21 mg/hr because of lipid load (after initial control, dose reduction may be necessary).

<sup>c</sup>In patients for whom the agent is rapidly titrated, consider dose reduction after response is achieved, given the agent's long half-life.

ACEI = angiotensin-converting enzyme inhibitor; D<sub>1</sub> = dopamine-1; IM = intramuscular; IV = intravenous; PRN = as needed; q = every. Adapted with permission from: Benken ST. Acute cardiac care. In: Abel EE, Bauer SR, Benken ST, et al, eds. Updates in Therapeutics: Critical Care Pharmacy Preparatory Review Course, 2017 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017.

target-organ damage. Data directly implicating sodium nitroprusside in increasing ICP are absent, but case reports have shown an association between ICP increases and sodium nitroprusside use (Anile 1981; Griswold 1981; Cottrell 1978). The theory claims that sodium nitroprusside dilates large-capacitance vessels (including large cerebral vessels), leading to vasodilation that may increase blood volume, which would subsequently increase ICP and potentially decrease CPP [note: CPP = MAP – ICP] (Rhoney 2009).

Because alternative agents (e.g., dihydropyridine calcium channel blockers [CCBs]) do not have this large-capacitance vessel property, use of sodium nitroprusside is cautioned in populations in which ICP elevations are present or may develop (e.g., acute stroke). In addition to the PD concerns with sodium nitroprusside, potential accumulation of toxic metabolites is a concern. Sodium nitroprusside contains cyanide molecules that are released during administration. Under normal circumstances, the cyanide that is released is bound by methemoglobin-forming cyanomethemoglobin (Rhoney 2009). The remaining cyanide molecules are converted to thiocyanate by transsulfuration in the liver, which is then excreted in the urine by the kidneys. Patients with chronic liver disease, alcoholism, and malnourishment may have a decreased capacity for transsulfuration, leading to an impaired ability to detoxify cyanide (Kwon 2009; Villanueva 2006; Kim 2003).

Signs of cyanide accumulation include decreased mental status, headache, vomiting, agitation, lethargy, coma, tachyarrhythmias, tachypnea, blood pressure lability, unexplained lactic acid, anion gap, metabolic acidosis, shock, and death (Johanning 1995). Although cyanide accumulation is a risk with sodium nitroprusside, under normal conditions, patients can detoxify 50 mg of sodium nitroprusside, which will then require doses greater than 10 mcg/kg/minute for more than 16 hours for greater than 10% methemoglobinemia (i.e., toxicity) (Rhoney 2009). Of note, a boxed warning exists regarding cyanide exposure, with a recommendation to avoid maximum doses (i.e., 10 mcg/kg/minute) for more than 10 minutes, especially in patients at risk of accumulation, as noted earlier. High doses are rarely used in clinical practice; therefore, cyanide toxicity is unlikely in most patients during the acute treatment phase. If toxicity is in question, carboxyhemoglobin and/or methemoglobin serum concentrations can be sent in addition to laboratory tests to elucidate lactic acidosis, and arterial and venous blood gases can be obtained to compare the  $P_{O_2}$  gradient (e.g., narrowing of venous-arterial  $P_{O_2}$  that occurs with cyanide toxicity). Cyanide concentrations are usually not processed at most institutions and serve mainly as confirmatory.

If cyanide toxicity is suspected, discontinuation of sodium nitroprusside is recommended, together with treatment with either intravenous hydroxycobalamin and sodium thiosulfate or sodium nitrite and sodium thiosulfate (Mokhlesi 2003; Hall 1987). Thiocyanate accumulation may cause toxicity but is considered less toxic than cyanide. In addition, thiocyanate

has a long half-life (3–7 days), which requires high doses (usually greater than 3 mcg/kg/minute) and extensive treatment durations (greater than 72 hours) to accumulate. Signs of thiocyanate toxicity are relatively nonspecific but may include fatigue, tinnitus, nausea, vomiting, hyperreflexia, altered mental status, and miosis (Rhoney 2009; Johanning 1995). Given the relative nonspecific signs of thiocyanate toxicity, serum concentration assays can be beneficial if processed in a time-sensitive fashion. Because thiocyanate is eliminated by the kidneys, caution is warranted for prolonged use in patients with acute renal failure who present with target-organ damage in hypertensive emergency, though short-term use (less than 24 hours) should be safe (Adebayo 2015; Ram 2009). If thiocyanate accumulation is suspected, management strategies include discontinuing the sodium nitroprusside infusion, using supportive care, or using hemodialysis to enhance clearance (Nessim 2006).

One last consideration is the relative cost of sodium nitroprusside. In recent years, the cost per vial of sodium nitroprusside has considerably increased by around 200% in some instances. Although generic products are becoming more available, cost analyzes are vital in evaluating the use of these products on a larger scale. One such analysis showed a yearly reduction of around \$300,000 in 1 year at one institution by converting postoperative use of sodium nitroprusside to clevidipine in an isolated treatment population (e.g., cardiac surgery) (Cruz 2016). Continuing analyzes such as this should be performed in this era of considerable drug inflation.

Because of the aforementioned concerns surrounding the use of sodium nitroprusside as a first-line agent, other agents have been investigated extensively. The CCBs are one such class of medications and include the dihydropyridine intravenous agents nicardipine and clevidipine and the non-dihydropyridine agents diltiazem and verapamil (Rhoney 2009). The dihydropyridine agents are peripherally selective L-type CCBs that exert their antihypertensive effects by inhibiting calcium influx through calcium channels along the vascular smooth muscle. This inhibition prevents smooth muscle contractility, leading to vasodilation and reduction in systemic blood pressure. These agents preferentially bind to peripheral L-type calcium channels in the cerebral, coronary, peripheral, and renal vascular smooth muscle (Fugit 2000; Sabbatini 1995). In contrast, the non-dihydropyridine agents diltiazem and verapamil have preferential effects in the heart in the order of the conduction systems and contractile myocardial cells in addition to their peripheral effects. Because of these negative inotropic and chronotropic effects, these agents are usually only used for select presentations of hypertensive crisis. When comparing the dihydropyridine CCBs with sodium nitroprusside, these agents do not affect ICP and may be considered preferential for patients with acute stroke as the target-organ damage on presentation of hypertensive emergency (Hemphill 2015; Gaab 1985).

The dihydropyridine CCBs are usually well tolerated with limited adverse effects. The most common adverse events associated with nicardipine are related to vasodilation, including headache, nausea, vomiting, and tachycardia (Curran 2006). Nicardipine is metabolized through CYP isoenzymes CYP3A4, CYP2C8, and CYP2D6, which may lead to prolonged clinical effects and more pronounced adverse effects in patients being treated for hypertensive emergency who have chronic liver disease (Frye 2006; Branch 1998). Clevidipine is an ultra-rapid-onset (see Table 1-5) dihydropyridine CCB that undergoes rapid inactivation by organ-independent metabolism through ester hydrolysis (Ericsson 1999). Clevidipine is formulated in a lipid emulsion and is contraindicated in patients with an allergy to soybeans, soy products, eggs, egg products, or those with defective lipid metabolism. Because of the lipid load associated with infusion, it is recommended to give less than 1000 mL of clevidipine per 24-hour period (average of 21 mg/hour) with consideration of triglyceride monitoring and coadministration of other lipid emulsions. Because lipid emulsions can serve as a growth medium for bacteria, clevidipine vials should be discarded after 12 hours of being punctured. Similar to nicardipine, clevidipine is well tolerated with minimal adverse effects. These adverse effects, again, include those largely related to vasodilation: headache, nausea, vomiting, and tachyarrhythmias as well as fever. Finally, nicardipine is about one-third the cost of clevidipine, which is about one-fourth the cost of sodium nitroprusside per vial. Although clinical considerations often supersede cost considerations, in the era of cost containment and reimbursement uncertainty, drug costs are very important considerations.

Contrary to the afterload effects that occur with the dihydropyridine CCBs, nitroglycerin is primarily a venous vasodilator, yet dose-dependent afterload reduction is attainable (Varon 2008). Because of the rapid venous vasodilation with nitroglycerin, it can reduce relative venous return and subsequently myocardial preload (Ignarro 2002). In addition to the peripheral effects of nitroglycerin, coronary artery vasodilatory effects occur without the complication of coronary steal (Adebayo 2015; Mann 1978). One key consideration with the clinical use of nitroglycerin is the tachyphylaxis that occurs, possibly because of sulfhydryl depletion (because of the lack of a nitrate-free interval), requiring frequent escalations in dosing to maintain hemodynamic effects (Hirai 2003; Larsen 1997; Needleman 1975). This tachyphylaxis usually occurs over the first 24–48 hours, and if intravenous blood pressure control is still required at those time intervals, additional or alternative agents may be warranted. In addition, by rapid escalations in dosing, patients become more at risk of the potential adverse effects of nitroglycerin, including flushing, headache, erythema, nausea, and vomiting.

$\beta$ -Antagonists (i.e.,  $\beta$ -blockers) are another drug class that can be used for hypertensive emergencies. The intravenous formulations that are available and used for this

indication include the  $\beta$ -selective antagonists esmolol and metoprolol and the combination  $\alpha_1$ - and  $\beta$ -antagonist labetalol (Rhoney 2009). Esmolol has preferential PK parameters of the  $\beta$ -antagonists—namely, the rapid onset, organ-independent metabolism through ester hydrolysis and short duration of activity leading to titratability (Singh 1992; Gray 1988). Metoprolol has  $\beta$ -selectivity similar to esmolol, but given its slower onset, intravenous push administration, and longer duration of activity, metoprolol has less titratability and can lead to extended, overaggressive, unintentional correction, placing patients at risk of induced ischemic complications (Bertel 1987; Reed 1986; Strandgaard 1984; Bannan 1980). Intravenous metoprolol is thus often avoided for this indication. Because of their  $\beta$ -selectivity, neither of these agents has direct vasodilatory effects, and blood pressure control is solely through the negative inotropic and chronotropic effects (Melandri 1987; Bourdillon 1979). Labetalol is a combination  $\alpha_1$ - and  $\beta$ -antagonist, which, according to the prescribed labeling, in intravenous formulation, primarily exerts its hemodynamic effects through the  $\beta$ -antagonist properties, given that the ratio of  $\alpha_1$  to  $\beta$  is about 1:7 compared with 1:3 in the oral formulation. Of interest, though labetalol is often given by continuous infusion, its PK profile better supports intravenous bolus administration. Early studies of high-dose (1 mg/kg, or 50 mg) intravenous bolus dosing compared with continuous intravenous infusions showed a better safety profile with continuous infusions, leading to the conclusion that labetalol should be given as a continuous infusion (Cumming 1979a; Cumming 1979b). This data should be cautiously interpreted as the intravenous bolus dosing at the time was much larger than dosing that is now considered standard and safe. Although continuous infusion labetalol is considered safe, overaggressive, unintentional correction has been reported when labetalol is used in this manner (Malesker 2012; Fahed 2008; Jivraj 2006). Because of the extended duration of action (see Table 1-5), each dose should be titrated cautiously. Of note, labetalol is one of the medications of choice for pregnancy-related hypertensive crisis. All  $\beta$ -antagonists must be avoided in patients with acute presentations of systolic heart failure for whom the negative inotropic effects could be harmful.

Hydralazine is a peripheral arterial vasodilator best known in this clinical setting for its safety in pregnancy (Sibai 2014; ACOG 2013; Vidaeff 2005). Hydralazine can be delivered either by intravenous or intramuscular injection at similar doses (Rhoney 2009). However, caution should be used, given the agent's suboptimal PK profile (see Table 1-5), unpredictable duration of effect on blood pressure (O'Malley 1975), and reports of inducing rebound tachycardia (Rhoney 2006).

Enalaprilat is an intravenous angiotensin-converting enzyme (ACE) inhibitor. According to the package insert, mechanistically, enalaprilat blocks the potent vasoconstriction of angiotensin II (AT2) by inhibiting the conversion of AT2 from angiotensin I. Given the PK profile (see Table 1-5) of enalaprilat, its usefulness in hypertensive emergency is

## Patient Care Scenario

A.G. is a 48-year-old man with no significant medical history. He presents with a stabbing sensation in his middle back and additional pain in his chest. His social history includes cigarette smoking, 1 pack/day, for the past 15 years. Chest radiography in the ED reveals mediastinal widening. Cardiac enzymes are within normal limits.

The patient's laboratory test results include Na 142 mEq/L, K 3.8 mEq/L, SCr 0.82 mg/dL, glucose 142 mg/dL,

total bilirubin 0.7 mg/dL, and ALT 31 U/L. He is rushed for a chest CT with angiography, which reveals an acute type B aortic dissection. His vital signs include blood pressure 210/122 mm Hg and heart rate 130 beats/minute.

Determine the appropriate management for A.G., including classification, goal(s), and treatment modalities.

### ANSWER

First, determine whether A.G. has signs or symptoms of target-organ damage. The patient's physical examination and presenting symptoms will lead toward which diagnostic tests and laboratory assays to obtain. The laboratory values do not indicate specific target-organ damage. Diagnostic evaluation with the chest CT with angiography reveals target organ damage of an acute type B aortic dissection. A.G. qualifies for a hypertensive emergency warranting intravenous therapy and ICU admission. Second, determine whether A.G. is an exception to the general treatment principles of hypertensive emergency. (Patients with those exceptions include acute strokes; pregnancy-associated acute, severe hypertension; and aortic dissection.) Type B aortic dissections are medical

emergencies and need to be treated as such. In addition, with acute aortic dissections, the goals change to targeting heart rate reduction to a goal heart rate of less than 60 beats/minute as well as blood pressure reduction to SBP less than 120 mm Hg (ideally, less than 100 mm Hg). Continuous infusion  $\beta$ -blockers are generally accepted as the initial medications of choice, and because of the PK/PD of esmolol compared with labetalol, esmolol may be preferred for initial therapy. If further reduction in blood pressure is needed after achieving heart rate control, any arterial vasodilator can be used, including nicardipine, clevidipine, or sodium nitroprusside, with preference given to agents that are readily titratable if signs/symptoms of overaggressive, unintentional correction occur.

1. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. *Circulation* 2010;121:1544-79.
2. Johnson W, Nguyen ML, Patel R. Hypertension crisis in the ED. *Cardiol Clin* 2012;30:533-43.
3. Papaioannou TG, Stefanadis C. Vascular wall shear stress: basic principles and methods. *Hellenic J Cardiol* 2005;46:9-15.

minimal. Beyond having a relatively slow onset, there can be delays in peak effects of up to 4 hours after administration (Rhoney 2009). A bolus dose may last 12–24 hours, making dose adjustment difficult and raising significant safety concerns. In addition, enalaprilat must be avoided in pregnant patients, and use may be associated with deterioration of renal function, especially in states of poor renal perfusion that potentially occur in hypertensive emergency, warranting avoidance or great caution with renal impairment.

Phentolamine is a peripheral  $\alpha_1$  and  $\alpha_2$  receptor antagonist leading to direct vasodilation. In general, phentolamine is reserved for catecholamine-excess presentations of hypertensive emergency (e.g., cocaine induced, pheochromocytoma, amphetamine induced). Because of the mechanism of phentolamine, adverse effects such as flushing and headache are common (Rhoney 2009; Chobanian 2003). In addition, rebound tachycardia can occur, which can lead to an oxygen supply-and-demand mismatch in patients with coronary artery disease, inducing angina or myocardial infarction (Grossman 1998).

Finally, fenoldopam is a peripherally acting dopamine-1 (D<sub>1</sub>) receptor agonist with activity in the coronary, renal (both afferent and efferent), mesenteric, and peripheral arteries. Fenoldopam has an appealing PK profile (see Table 1-5), but

it has been associated with increased intraocular pressure, and caution should be used in patients with concerns for ICP elevations (Rhoney 2009). In addition, fenoldopam contains sodium metabisulfite, which can trigger anaphylactic reactions in those with sulfa or sulfite allergies. Common adverse effects of fenoldopam include headache, nausea, vomiting, and flushing as well as inducing tachycardia; of note, fenoldopam may cause hypokalemia.

### Comparative Data in Hypertensive Emergency

Because systematic review has failed to show major clinical outcome differences between agents, other considerations, including safety profile and other markers of efficacy (e.g., percent attainment of goal, need for other blood pressure agents), will distinguish the agents from one another. Table 1-6 highlights some of the key findings of analyses comparing agents for hypertensive emergency.

Given these data, some conclusions can be made about specific agent comparisons. For example, nicardipine is more dependable than labetalol with respect to faster time to blood pressure goal attainment, more time spent within blood pressure goal range, decreased number of rescue medications and titrations needed to achieve target blood pressure, and better BPV profile. Despite these advantages, no clinical

**Table 1-6.** Comparative Data for Agents in Hypertensive Emergency

Agents Compared	Population	Study Design	Key Findings
Nicardipine vs. labetalol <sup>a</sup>	Mixed ICU population Treat if SBP > 160 mm Hg or DBP > 90 mm Hg n=382	Retrospective consecutive	No difference in magnitude of average change in SBP or DBP Greater proportion meeting BP target with nicardipine (83%) vs. labetalol (67%) (p=0.04) Lesser proportion needing additional BP agents with nicardipine (17%) vs. labetalol (31%) (p=0.02) Less hypotensive events (10% vs. 19%, p=0.04) and bradycardia/AV block, p=0.03) with nicardipine vs. labetalol
Nicardipine vs. labetalol <sup>b</sup>	Patients with stroke with acute hypertension (54% ICH, 22% SAH, 23% AIS) n=90	Retrospective, consecutive	Lower number of dose adjustments to achieve goal (2 vs. 4; p<0.001) with nicardipine Decreased need to add additional agents (8% vs. 33%; p<0.013) with nicardipine Significantly less BPV [SD-SBP] (8.19 vs. 10.78 mm Hg; p=0.003) with nicardipine In patients with ICH, greater goal attainment at 60 min (33% vs. 6%; p=0.02) with nicardipine
Nicardipine vs. labetalol <sup>c</sup>	Patients with stroke with acute hypertension ICH (54%) – Treated if SBP > 180 mm Hg SAH (11%) – Treated if SBP > 160 mm Hg AIS (35%) –Treated if SBP > 185 mm Hg to give tPA or > 220 mm Hg (no tPA)	Prospective, pseudo-randomized	Greater attainment of blood pressure goal (100% vs. 61%; p<0.001) with nicardipine More consistent goal attainment at 60 min (89% vs. 25%; p<0.001) with nicardipine Greater % of time spent within goal (89% vs. 36%; p<0.001) with nicardipine Significantly less BPV [SD-SBP] (15 vs. 19 mm Hg; p<0.001) with nicardipine
Nicardipine vs. sodium nitroprusside <sup>d</sup>	ICH n=1426	Retrospective, database query	Use of sodium nitroprusside associated with significantly higher multivariate-adjusted mortality (OR 1.6 [1.2–2.1]; p=0.001)
Nicardipine vs. sodium nitroprusside <sup>e</sup>	Postoperative: 1) Cardiac surgery – Treat if SBP ≥ 140 mm Hg or DBP ≥ 95 mm Hg 2) Non-cardiac surgery – Treat if SBP ≥ 20% single preoperative value (and SBP ≥ 140 mm Hg or DBP ≥ 95 mm Hg) or SBP ≥ 200 mm Hg or DBP ≥ 110 mm Hg n=139 enrolled, 117 analyzed	Prospective, multicenter, randomized	No difference in BP attainment between agents in either group (i.e., cardiac or non-cardiac surgery) More rapid attainment of therapeutic response with nicardipine (14 +/- 1 min) vs. sodium nitroprusside (30.4 +/- 3.5 min) (p=0.0029) Patients receiving nicardipine required fewer dose changes to attain goal (1.5 +/- 0.2 changes 5.1 +/- 1.4 [p<0.05]) No differences in adverse effects between agents
Nicardipine vs. sodium nitroprusside <sup>f</sup>	Hypertensive crisis and acute pulmonary edema n=40	Prospective	No time-dependent differences in BP reduction between groups No mention of adverse effects
Nicardipine vs. esmolol <sup>g</sup>	Emergency hypertension after craniotomy Treat if SBP > 130 mm Hg with goal of SBP < 140 mm Hg for first 24 hr n=52	Prospective, randomized, open-label	Fewer treatment failures with nicardipine vs. esmolol (5% vs. 55%; p=0.0012) *Fewer patients randomized to nicardipine needed additional BP-controlling agents than did those randomized to esmolol

(Continued)

**Table 1-6.** Comparative Data for Agents in Hypertensive Emergency (*continued*)

Agents Compared	Population	Study Design	Key Findings
Nicardipine vs. nitroglycerin <sup>h</sup>	Postoperative acute hypertension after CABG Goal SBP < 110 mm Hg n=20	Prospective, randomized, open-label	BP decreased sooner in patients on nicardipine (7.7 hr) vs. nitroglycerin (11.9 hr) achieving a lower average SBP (94 mm Hg vs. 108 mm Hg) compared with nitroglycerin (p<0.05) No differences in clinical outcomes or adverse effects
Nicardipine vs. clevidipine <sup>i</sup>	Neurosciences ICU patients (e.g., ICH, ischemic stroke, tumor resection, encephalopathy, hydrocephalus, seizure, cerebral edema, ventriculoperitoneal shunt removal, transient ischemic attack, and elective procedures) n=57	Retrospective	No statistical differences in time to target SBP attainment between nicardipine (46 min) and clevidipine (30 min) (p=0.13) No differences in time spent within the target BP range between agents Nicardipine associated with significantly higher volume with infusion (1254 mL vs. 530; p=0.02)
Clevidipine vs. nitroglycerin, sodium nitroprusside, and nicardipine <sup>j,k</sup>	Perioperative acute hypertension before, during, or after cardiac surgery n=1512	Prospective, randomized, open-label, parallel comparison	No difference in clinical outcomes in incidence of myocardial infarction, stroke, or renal dysfunction Clevidipine associated with greater time in goal range than nitroglycerin (p=0.0006) and sodium nitroprusside (p=0.003) Clevidipine associated with a better BPV profile than the other agents (p=0.0004)
Clevidipine vs. standard of care (nitroglycerin and nicardipine) <sup>l</sup>	ED hypertensive emergency (SBP > 160 mm Hg) with dyspnea and acute heart failure n=104	Prospective, randomized, open-label	Achieved higher percentage of target BP attainment with clevidipine (71%) than with SOC (37%) (p=0.002) Lesser need for additional BP agents with clevidipine (16%) than with SOC (51%) (p=0.0005) Greater improvement in dyspnea (p=0.02) and faster attainment of target BP (p=0.0006) with clevidipine
Clevidipine vs. sodium nitroprusside <sup>m</sup>	Postoperative acute hypertension after CABG Treat if MAP > 90 mm Hg for at least 10 min to goal range of MAP to 70–80 mm Hg	Prospective, randomized	No difference in ability to control MAP between agents No difference in number of total dose adjustments to achieve goal BP
Labetalol vs. sodium nitroprusside <sup>n</sup>	Malignant hypertension (severely elevated BP + grade III or IV retinopathy) or hypertensive encephalopathy n=15	Prospective, consecutive, open-label	Equal attainment of BP goal within 60 min in both groups with similar reductions in MAP With labetalol, lesser percent decrease in systemic vascular before and after therapy than with sodium nitroprusside (p<0.05) Reduction rate in middle cerebral artery blood velocity smaller with labetalol than with sodium nitroprusside (p<0.05) May be a preferential difference in blood flow to systemic circulation compared with cerebral circulation with sodium nitroprusside (i.e., decreased cerebral blood flow)

**Table 1-6.** Comparative Data for Agents in Hypertensive Emergency (continued)

Agents Compared	Population	Study Design	Key Findings
Labetalol vs. nicardipine <sup>o</sup>	ED hypertensive crisis (63.3% hypertensive emergency) Treat if SBP > 180 mm Hg x 2 n=226	Prospective, multicenter, randomized	30-min attainment of target BP goal occurred less commonly with labetalol (82.5%), nicardipine (91.7%) (p=0.0039) Patients receiving nicardipine were more likely to be in goal range 30 min after adjustment for confounders (OR 2.73; p=0.028) No difference in the need for rescue agents
Labetalol vs. nicardipine <sup>p</sup>	Aneurysmal subarachnoid hemorrhage Goal MAP 70–110 mm Hg n=103	Retrospective, consecutive	Labetalol associated with a shorter % of time within MAP goal range (58% vs. 78%; p=0.001) No difference in BP variability (SD-MAP; p=0.137) Labetalol associated with a slower response (p=0.005) and more treatment failures (28% vs. 0%, p<0.001)
Labetalol vs. hydralazine <sup>q</sup>	Hypertensive crisis in pregnant (24 wks' gestation or more) patients: (74% severe preeclampsia, ~12% chronic HTN with superimposed preeclampsia, ~12% chronic HTN, 1.5% eclampsia) Treat if SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg n=261	Prospective, randomized	No difference in BP control efficacy determined by achieving SBP, DBP, and MAP goal No difference in need for rescue therapy or adverse effects
Labetalol vs. hydralazine <sup>r</sup>	Severe hypertension associated with pregnancy (~55% severe preeclampsia, ~18% gestational HTN, 15% chronic HTN with superimposed preeclampsia, 1.5% with eclampsia) Treat if SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg n=200	Prospective, randomized	No difference in attainment of BP goals More maternal palpitations (p=0.01), tachycardia (p<0.05) with hydralazine than with labetalol More neonatal bradycardia (p=0.008) and hypotension (p<0.05) with labetalol than with hydralazine

<sup>o</sup>Malesker MA, Hilleman DE. Intravenous labetalol compared with intravenous nicardipine in the management of hypertension in critically ill patients. *J Crit Care* 2012;27:528.e7-14.

<sup>p</sup>Liu-DeRyke X, Janisse J, Coplin WM, et al. A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care* 2008;9:167-76.

<sup>q</sup>Liu-DeRyke X, Levy PD, Parker D Jr, et al. A prospective evaluation of labetalol versus nicardipine for blood pressure management in patients with acute stroke. *Neurocrit Care* 2013;19:41-7.

<sup>r</sup>Suri MF, Vazquez G, Ezzeddine MA, et al. A multicenter comparison of outcomes associated with intravenous nitroprusside and nicardipine treatment among patients with intracerebral hemorrhage. *Neurocrit Care* 2009;11:50-5.

<sup>s</sup>Halpern NA, Goldberg M, Neely C, et al. Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992;20:1637-43.

<sup>t</sup>Yang HJ, Kim JG, Lim YS, et al. Nicardipine versus nitroprusside infusion as antihypertensive therapy in hypertensive emergencies. *J Int Med Res* 2004;32:118-23.

<sup>u</sup>Bebawy JF, Houston CC, Kosky JL, et al. Nicardipine is superior to esmolol for the management of postcraniotomy emergence hypertension: a randomized open-label study. *Anesth Analg* 2015;120:186-92.

<sup>v</sup>Vecht RJ, Swanson KT, Nicolaidis EP, et al. Comparison of intravenous nicardipine and nitroglycerin to control systemic hypertension after coronary artery bypass grafting. *Am J Cardiol* 1989;64:19H-21H.

<sup>w</sup>Finger JR, Kurczewski LM, Brophy GM. Clevidipine versus nicardipine for acute blood pressure reduction in a neuroscience intensive care population. *Neurocrit Care* 2017;26:167-73.

**Table 1-6.** Comparative Data for Agents in Hypertensive Emergency (*continued*)

(Continued)

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- <sup>6</sup>Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the ED. *Crit Care* 2011;15:R157 (page 1-8).
- <sup>7</sup>Woloszyn AV, McAllen KJ, Figueroa BE, et al. Retrospective evaluation of nicardipine versus labetalol for blood pressure control in aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2012;16:376-80.
- <sup>8</sup>Delgado De Pasquale S, Velarde R, Reyes O, et al. Hydralazine vs. labetalol for the treatment of severe hypertensive disorders of pregnancy. A randomized, controlled trial. *Pregnancy Hypertens* 2014;4:19-22.
- <sup>9</sup>Vigil-De Gracia P, Lasso M, Ruiz E, et al. Severe hypertension in pregnancy: hydralazine or labetalol: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 2006;126:157-62.
- AIS = acute ischemic stroke; AV = atrioventricular, CABG = coronary artery bypass grafting; HTN = hypertension; SOC = standard of care; tPA = tissue plasminogen activator.

differences are associated with using nicardipine over labetalol. Additional conclusions support the cautioned use of sodium nitroprusside for hypertensive emergencies presenting with neurologic injury. Furthermore, clevidipine may have a better blood pressure variability profile than nitroglycerin or sodium nitroprusside, lead to a lesser volume administered than nicardipine, and allow potentially faster attainment of blood pressure goals than the other agents. Again, however, despite these advantages, major clinical outcomes have not been affected. Finally, in pregnancy-associated severe hypertension, labetalol may be associated with fewer maternal adverse effects than hydralazine, but the agents' impact on fetal or maternal clinical outcomes may not differ.

### **Guideline Recommendations and Consensus Opinions for Unique Presentations of Hypertensive Emergency**

Because robust studies supporting one agent over another regarding clinical outcomes are lacking, several medications can be used for the various presentations of hypertensive emergency. Understanding the safety profiles of each medication and data published in comparative studies (see Table 1-6) is important. Table 1-7 lists the individual agents, potential indications, and key considerations for use.

Current available guidelines and consensus opinions support the data synthesized in Table 1-7. International guidelines for the medical management of acute aortic dissection recommend  $\beta$ -blockers to reduce the force of ventricular ejection (which can worsen shear stress) and, if additional blood pressure lowering is needed to meet the goal of SBP less than 120 mm Hg (ideally less than 100 mm Hg), use of a vasodilator

(Erbel 2014; JCS Joint Working Group 2013; Hiratzka 2010; Erbel 2001). For acute ischemic stroke, the guidelines do not recommend a single specific agent or class of agents but state that an individualized approach is most appropriate, with consideration of agents such as labetalol, nicardipine, hydralazine, and enalaprilat (Jauch 2013). Given the benefit of nicardipine and clevidipine compared with the other agents with respect to BPV, these agents may be considered preferential. Regarding acute hemorrhagic stroke (e.g., ICH), the guidelines are silent on which agents to use for the early aggressive reduction in patients who would qualify for such aggressive reductions (see earlier text in Treatment Goals: Acute Hemorrhagic Stroke section) of blood pressure, but referenced literature in the guidelines predominantly used nicardipine as a primary agent (Hemphill 2015). In addition, because of the importance of BPV in this population, nicardipine and clevidipine may be considered preferential agents in this population.

In the guidelines for patients with acute, severe hypertension related to pregnancy, specific agents (hydralazine, labetalol, and CCBs [e.g., nicardipine]) are recommended. Comparisons between these agents have failed to show superiority; thus, the guidelines recommend selecting an agent on the basis of adverse effects, contraindications, and clinician experience with that agent (ACOG 2013). For patients with cocaine-induced hypertension, benzodiazepines are an effective first-line therapy, but additional blood pressure control may be warranted (Richards 2006). When additional blood pressure control is needed,  $\alpha$ -blocking agents (e.g., phentolamine), dihydropyridine CCBs (e.g., nicardipine and clevidipine), and nitric oxide-mediated vasodilators (e.g., sodium nitroprusside and nitroglycerin) are effective but may

**Table 1-7.** Indications and Special Considerations for Medications Used for Hypertensive Emergency

Medication	Indication(s)	Special Considerations
Hydralazine	Pregnancy	Can result in prolonged hypotension, given longer half-life Risk of reflex tachycardia Headaches, lupuslike syndrome (more likely with long-term use)
Nitroglycerin	Coronary ischemia or infarction Acute left ventricular failure Pulmonary edema	Tachyphylaxis occurs rapidly, requiring frequent dose titrations Adverse effects: Flushing, headache, erythema, often dose limiting Venous greater than arterial vasodilator
Sodium nitroprusside	Most indications (excluding ICP elevations and coronary infarction/ ischemia)	Liver failure – Cyanide accumulation Renal failure – Thiocyanate accumulation Can obtain serum cyanide and thiocyanate concentrations Toxicity associated with prolonged infusions (> 72 hr) or high doses (> 3 mcg/kg/min) May result in coronary steal Increases ICP
Clevidipine	Acute ischemic or hemorrhagic stroke	Formulated in oil-in-water formulation providing 2 kcal/mL of lipid calories Caution for patients with soy or egg allergy Risk of reflex tachycardia
Nicardipine	Acute ischemic or hemorrhagic stroke	Risk of reflex tachycardia Infusion can lead to large volumes administered
Esmolol	Aortic dissection Coronary ischemia/infarction	Contraindicated in acute decompensated heart failure Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate esmolol first because of its delayed onset relative to vasodilators such as sodium nitroprusside) Metabolism is organ-independent (hydrolyzed by esterases in blood) Useful in tachyarrhythmias
Labetalol	Acute ischemic or hemorrhagic stroke Aortic dissection Coronary ischemia/infarction Pregnancy	May be used as monotherapy in acute aortic dissection Contraindicated in acute decompensated heart failure Prolonged hypotension may occur with overtreatment; dose cautiously $\alpha/\beta = 1/7$
Metoprolol	Aortic dissection Coronary ischemia/infarction	Contraindicated in acute decompensated heart failure Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate metoprolol first because of its delayed onset relative to vasodilators such as sodium nitroprusside) Useful in tachyarrhythmias
Enalaprilat	Acute left ventricular failure	Contraindicated in pregnancy Cautious dosing; prolonged duration of action
Phentolamine	Catecholamine excess (e.g., pheochromocytoma)	Use in catecholamine-induced hypertensive emergency If used for cocaine-induced HTN crisis – Use in conjunction with BZDs
Fenoldopam	Most indications	Caution with increases in ICP or intraocular pressure Risk of reflex tachycardia Can cause hypokalemia, flushing; can worsen glaucoma Unique MOA: $D_1$ specific agonist – Peripheral vasodilation

BZD = benzodiazepine; ICP = intracranial pressure; MOA = mechanism of action.

Adapted with permission from: Benken ST. Acute cardiac care. In: Abel EE, Bauer SR, Benken ST, et al, eds. Updates in Therapeutics: Critical Care Pharmacy Preparatory Review Course, 2017 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017.

## Practice Points

- The first step in assessing a patient for hypertensive crisis is determining the presence or absence of target-organ damage.
- Target-organ damage assessment often stems from patient-specific chief concerns, physical examination findings, routine and directed laboratory test assessments, and use of diagnostic examinations.
- After patients are confirmed to have a hypertensive emergency, they must be screened for exceptions (e.g., stroke, pregnancy-associated acute hypertension, and aortic dissection) to the general principles of treatment, which will allow for target goal development.
- In general hypertensive emergencies (i.e., without exceptions), the goal in the first 60 minutes of treatment is to reduce the MAP by 25%.
- Patients with exceptions have unique treatment goals leading to unique medication selection.
- The goal of medication selection is to provide “smooth” blood pressure reduction, optimizing BPV with agents that are readily titrated while avoiding complications because of adverse effects.
- Knowledge of the PK, PD, hemodynamics, and adverse effect profiles of the available options is warranted.

be limited because of a lack of control of concurrent tachycardia. If concurrent tachycardia is present, added combination  $\alpha/\beta$ -blockers (e.g., labetalol) are safe and effective (Richards 2006).  $\beta$ -Selective antagonists should be avoided as initial monotherapy. In addition, for patients with hypertensive emergency caused by pheochromocytoma, phentolamine is largely considered the drug of choice (Prejbisz 2011).

Finally, for acute presentations of heart failure (e.g., left heart failure with pulmonary edema or right heart failure with systemic edema), nitroglycerin is the drug of choice because it can rapidly decrease preload, providing rapid symptom relief and, at higher doses, can also decrease afterload. Concurrent loop diuretics should also be administered with considerations for renal replacement therapy, as needed, for volume removal (Rhoney 2009).

## CONCLUSION

The treating clinician needs to rapidly assess target-organ damage to differentiate hypertensive emergency from hypertensive urgency. In addition, the clinician must consider whether a patient qualifies as an exception to the general treatment principles of hypertensive emergency (compelling condition). Once the treatment goal is selected, medication is selected on the basis of treatment goals, presenting target-organ damage, PK and PD parameters of each medication, BPV profiles, and clinical data. Each patient will qualify for continuous monitoring to assess for achievement of target goal(s) and avoidance of overaggressive, unintentional correction. Furthermore, close monitoring is required to evaluate for adverse effects from the medications selected.

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# Self-Assessment Questions

## Questions 1–3 pertain to the following case.

A.B. is a 58-year-old man with a medical history of allergic rhinitis. He presents to the ED for acute onset of shortness of breath, side pain, and blurred vision. A.B. denies illicit drug and cigarette use but confirms alcohol intake (2 drinks each night). Urine toxicology is negative. His vital signs include blood pressure 202/140 mm Hg, heart rate 83 beats/minute, respiratory rate 31 breaths/minute, and pain 4/10 (chest and side pain). His home drugs include cetirizine 10 mg orally once daily, aspirin 81 mg orally once daily, and a multivitamin 1 tablet orally once daily. A.B. confirms adherence to this regimen with no missed doses over the past 1½ years. His laboratory test results include SCr 0.8 mg/dL, AST 608 U/L, ALT 458 U/L, lipase 20 U/L, total bilirubin 1 mg/dL, direct bilirubin 0.4 mg/dL, BNP 50 pg/mL, and INR 1.8. Retinal examination results are within normal limits.

1. Which one of the following best explains A.B.'s presentation?
  - A. Acute illicit drug intoxication leading to liver injury and direct hepatic damage
  - B. Acute new-onset heart failure leading to hepatic congestion
  - C. Acute hypertension-induced microvascular thrombosis leading to hepatic hypoperfusion
  - D. Acute medication-induced hepatic insufficiency leading to transaminitis
2. Which one of the following is the best treatment goal for A.B.?
  - A. Reduce MAP to around 120 mm Hg within the first 60 minutes.
  - B. Reduce MAP to around 80 mm Hg within the first 60 minutes.
  - C. Reduce SBP less than 180 mm Hg within the first few hours.
  - D. Reduce SBP less than 140 mm Hg within the first few hours.
3. Which one of the following is best to recommend for A.B.?
  - A. Sodium nitroprusside continuous intravenous infusion
  - B. Hydralazine intravenous push every 8 hours
  - C. Clevidipine continuous intravenous infusion
  - D. Metoprolol intravenous push every 4 hours

## Questions 4–7 pertain to the following case.

J.J. is a 74-year-old woman (height 68 in, weight 70 kg) with a medical history of hyperlipidemia, gout, asthma, and hypertension. She presents to the ED with a throbbing headache that she labels as "the worst headache of her life." J.J. refuses to give a social history. She states that the pain started this morning

(about 6 hours ago) and seems to have reached a steady maximum but without improvement using OTC acetaminophen. J.J. is rushed for a CT of the head, which reveals a small intracerebral hemorrhage (ICH) with no mass effect that is deemed inoperable by neurosurgery. Her vital signs include blood pressure 214/108 mm Hg and heart rate 48 beats/minute.

4. Which one of the following best explains blood pressure variability (BPV) in the context of this presentation?
  - A. BPV has not been proven to be a valued consideration in this type of hypertensive crisis.
  - B. BPV target is equal to a SD-SBP less than 15 mm Hg because this is consistently correlated with positive ICH outcomes.
  - C. Large fluctuations in peak and nadir blood pressure should be avoided in this patient.
  - D. Medication-specific BPV profiles do not differ; thus, any agent can be chosen to manage this ICH.
5. Which one of the following is best to recommend as J.J.'s treatment goal?
  - A. SBP less than 160 mm Hg as soon as possible
  - B. MAP reduction by 25% over the first 60 minutes
  - C. MAP less than 130 mm Hg over the first 24 hours
  - D. SBP less than 180 mm Hg over the first 24 hours
6. The medical team updates you that J.J.'s head CT was misread and that it has been corrected to state: "large intracerebral hemorrhage with 5-mm midline shift." No medications have been initiated yet. Which one of the following changes is best to recommend for J.J.?
  - A. SBP less than 160 mm Hg as soon as possible
  - B. MAP reduction by 25% over the first 60 minutes
  - C. MAP less than 130 mm Hg over the first 24 hours
  - D. SBP less than 140 mm Hg over the first 24 hours
7. Which one of the following is best to recommend, given J.J.'s corrected CT reading?
  - A. Sodium nitroprusside continuous intravenous infusion
  - B. Fenoldopam continuous intravenous infusion
  - C. Labetalol continuous intravenous infusion
  - D. Clevidipine continuous intravenous infusion

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

E.T. is 44-year-old man with a medical history significant for hypertension. His social history is positive for 2 pack/day cigarette smoking and social alcohol consumption. E.T. presents to the ED 1 hour after experiencing some facial drooping and numbness and tingling of his right extremity. He is rushed for a CT scan; this rules out any acute hemorrhagic processes. E.T. is evaluated and is a candidate for intravenous tissue

plasminogen activator (tPA). His vital signs include blood pressure 194/112 mm Hg, heart rate 82 beats/minute, respiratory rate 20 breaths/minute, pain 4/10, and  $\text{Sao}_2$  97%.

8. Which one of the following is best to recommend regarding timing of E.T.'s blood pressure control?
  - A. Before and during tPA only
  - B. During and after tPA only
  - C. After tPA only
  - D. Before, during, and after tPA
9. Which one of the following is best to recommend to treat E.T.'s presentation?
  - A. Sodium nitroprusside continuous intravenous infusion
  - B. Nicardipine continuous intravenous infusion
  - C. Labetalol continuous intravenous infusion
  - D. Hydralazine intravenous push every 4 hours
10. A 52-year-old man with no significant medical history has a family history significant for diabetes and hypertension. His social history is negative. The patient presents to the ED with complaints of decreased urinary output, lethargy, and shortness of breath since last night. Diagnostics include head and chest CT scans (pulmonary embolus protocol), which are negative. Bedside echocardiography reveals normal heart function. Chest radiography is grossly normal. Laboratory test results show Hgb 10.1 g/dL, liver panel within normal limits, cardiac enzymes negative, and SCr 2.7 mg/dL (baseline 0.6 mg/dL). The patient's vital signs include pain 1/10, blood pressure 228/134 mm Hg, heart rate 86 beats/minute, respiratory rate 20 breaths/minute, and  $\text{Sao}_2$  98%. Which one of the following is best to recommend as a treatment goal for this patient?
  - A. SBP less than 140 mm Hg as soon as possible
  - B. HR less than 60 beats/minute and SBP less than 120 mm Hg (ideally less than 100 mm Hg) within minutes
  - C. SBP less than 160 mm Hg within the first 60 minutes
  - D. MAP less than 125 mm Hg within the first 60 minutes
11. Which one of the following patient scenarios is most likely to trigger a hypertensive emergency?
  - A. Patient has the diagnosis of chronic hypertension and some part of the medication adherence process (e.g., access to medication) fails.
  - B. Patient presents to the ED with a target-organ specific complaint as the first manifestation of chronic essential hypertension.
  - C. Patient develops the emergency in the hospital because of a lack of attention to detail in the inpatient, admission medication reconciliation process.
  - D. Patient presents with another complaint, usually infectious, that is the underlying trigger for the patient's emergency.

12. Your medical team is curious about applying BPV to its treatment algorithms for hypertensive emergency. Which one of the following educational points would be best to influence the team's clinical practice?
  - A. Absence of data to support BPV as a primary therapeutic target
  - B. Inability to effect the BPV; it is purely a patient-driven manifestation
  - C. No clinical usefulness or application of BPV
  - D. Only animal data showing any association with clinical outcomes
13. Which one of the following drugs would likely have the most favorable BPV profile?
  - A. Hydralazine
  - B. Labetalol
  - C. Clevidipine
  - D. Enalaprilat

**Questions 14 and 15 pertain to the following case.**

H.F. is 57-year-old man with a 20-year history of hypertension. He presents to the ED after being unable to fill or take his medications for 1 week because of financial hardships. His social history is positive for 1 pack/day cigarette smoking; he denies using illicit drugs or alcohol. H.F.'s current symptoms include significant shortness of breath, which is worse with lying down and exertion. Diagnostics include a chest CT scan (pulmonary embolus protocol), which is negative. Bedside echocardiography reveals depressed systolic heart function, and chest radiography reveals volume overload. H.F.'s laboratory test results include Hgb 8.1 g/dL, liver panel within normal limits, cardiac enzymes negative, SCr 1.9 mg/dL (baseline 1.2 mg/dL), and BNP 1200 pg/mL (baseline around 400 pg/mL). His vital signs include pain 3/10, blood pressure 210/120 mm Hg, heart rate 110 beats/minute, respiratory rate 28 breaths/minute, and  $\text{Sao}_2$  93%.

14. Which one of the following is the most appropriate treatment goal for H.F.?
  - A. MAP less than 112 mm Hg within the first 60 minutes
  - B. HR less than 60 beats/minute and SBP less than 120 mm Hg (ideally less than 100 mm Hg) within minutes
  - C. SBP less than 160 mm Hg within the first 60 minutes
  - D. MAP less than 125 mm Hg within the first 24 hours
15. Which one of the following is best to recommend for H.F.?
  - A. Nitroglycerin 10-mcg/minute continuous intravenous infusion
  - B. Sodium nitroprusside 0.3-mcg/kg/minute continuous intravenous infusion
  - C. Labetalol 0.5-mg/minute continuous intravenous infusion
  - D. Esmolol 50-mcg/kg/minute continuous intravenous infusion