# Hypertensive emergencies: an update

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**Purpose of review**

Systemic hypertension (HTN) is a common medical condition affecting over 1 billion people worldwide. One to two percent of patients with HTN develop acute elevations of blood pressure (hypertensive crises) that require medical treatment. However, only patients with true hypertensive emergencies require the immediate and controlled reduction of blood pressure with an intravenous antihypertensive agent.

**Recent findings**

Although the mortality from hypertensive emergencies has decreased, the prevalence and demographics of this disorder have not changed over the last 4 decades. Clinical experience and reported data suggest that patients with hypertensive urgencies are frequently inappropriately treated with intravenous antihypertensive agents, whereas patients with true hypertensive emergencies are overtreated with significant complications.

**Summary**

Despite published guidelines, most patients with hypertensive crises are poorly managed with potentially severe outcomes.

**Keywords**

aortic dissection, clevidipine, eclampsia, esmolol, hypertension, hypertensive emergencies, labetalol, nicardipine, pulmonary edema

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## Introduction

Systemic hypertension (HTN) is a common medical condition affecting over 1 billion people worldwide and more than 65 million Americans [1,2]. Although chronic hypertension is an established risk factor for cardiovascular, cerebrovascular and renal disease, acute elevations in blood pressure can result in acute end-organ damage with significant morbidity. Hypertensive emergencies and hypertensive urgencies (see definitions below) are commonly encountered by a wide variety of clinicians. Prompt recognition, evaluation and appropriate treatment of these conditions are crucial to prevent excessive morbidity. This article reviews our current understanding of hypertensive crises and highlights the common misconceptions and pitfalls in the diagnosis and management of these disorders.

## Definitions

The classification and approach to hypertension undergoes periodic review by the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure with the most recent report (JNC VII) having been released in 2003 [3,4]. With this report, the classification of blood pressure (BP) was simplified with the recognition of two stages of hypertension (compared to the previous four stages in JNC VI). In addition, a new category called prehypertension was added. Hypertension is defined as a SBP greater than 140 mmHg or a DBP greater than 90 mmHg in patients with known HTN or otherwise measured on two or more settings. Although not specifically addressed in the JNC VII report, patients with a SBP greater than 179 mmHg or a DBP greater than 109 mmHg are usually defined as having a 'hypertensive crisis'. The 1993 report of the JNC proposed an operational classification of hypertensive crises as either 'hypertensive emergencies' or 'hypertensive urgencies' [5]. This classification remains useful today. Severe elevations in BP were classified as 'hypertensive emergencies' in the presence of acute end-organ damage or as 'hypertensive urgencies' in the absence of acute target-organ involvement. Distinguishing hypertensive urgencies from emergencies is critical in formulating a therapeutic plan. Patients with hypertensive urgency should have their BP reduced within 24–48 h, whereas patients with a hypertensive emergency should have their BP lowered immediately, but not to 'normal' levels. The term 'malignant hypertension' has been used to describe a syndrome characterized by elevated BP accompanied by encephalopathy or acute nephropathy [3,6]. This term, however, has been removed from the National and International Blood Pressure Control guidelines and is best referred to as a hypertensive emergency.

'Hypertensive emergencies' were first described by Volhard and Fahr in 1914 [7]. They described patients with severe hypertension, accompanied by signs of vascular injury to the heart, brain, retina and kidney. This syndrome had a rapidly fatal course ending in heart attack, renal failure or stroke. It was not until 1939 when the first large study of the natural history of 'malignant hypertension'' was published [8]. The results of this seminal article by Keith *et al.* revealed that untreated malignant hypertension had a 1-year mortality of 79% with a median survival of 10.5 months. Prior to the introduction of antihypertensive medications, approximately 7% of hypertensives developed a hypertensive crisis [9].

**Key points**

- Hypertensive emergencies occur in up to 2% of patients with systemic hypertension (HTN).
- The mortality from hypertensive emergencies has decreased over the last 4 decades; however, the prevalence and demographics of these disorders have remained unchanged.
- Patients with hypertensive emergencies develop endothelial dysfunction that may persist for years after the acute event.
- Current evidence suggests that most patients with hypertensive emergencies receive inappropriate therapy with a high incidence of treatment-related adverse effects.
- A high percentage of hospitalized patients with accelerated HTN are inappropriately treated with intravenous antihypertensive agents with potentially serious sequelae.

## Epidemiology of hypertensive crises

In the United States, hypertensive crises continue to be common. The epidemiology of this disorder parallels the distribution of essential hypertension with a higher incidence among the elderly and African–Americans, with men being affected two times more frequently than women [10–12]. It has been estimated that hypertensive crises affect 500 000 Americans annually or approximately 1% of hypertensive adults [13,14]. This however may be an underestimate of the true prevalence. In the only prospective study conducted to date, Saguner *et al.* [15] followed 89 hypertensive patients for a mean of 1.6 years. In this study, 13 (15.3%) patients experienced a hypertensive crisis during follow-up; 84% had symptoms related to the acute increase in BP. Zampaglione *et al.* [16] evaluated the prevalence of hypertensive crises in an emergency department over 12 months in Turin, Italy. Hypertensive crises (76% urgencies and 24% emergencies) represented 3% of all the patient visits, but 27% of all medical emergencies. Longitudinal studies by Gonzalez *et al.* [17] and Lip *et al.* [18] suggest that the prevalence of hypertensive emergencies and the patient demographics have remained stable over the last four decades. In the largest prospective analysis to date, Lane *et al.* [19] followed 446 hypertensive emergencies with a total of 5700 person-years of observation and a median follow-up of 103.8 months. These authors reported a significant improvement in 5-year survival from 32.0% prior to 1977 to 91.0% for patients diagnosed between 1997 and 2006. The Studying the Treatment of Acute hypertension (STAT) is a 25-institution U.S. registry of 1588 patients with severe acute hypertension enrolled between January 2007 and April 2008 who were treated with intravenous therapy [20]. In the STAT registry, the hospital mortality was 6.9% with an aggregate 90-day mortality of 11% and a 90-day readmission rate of 37%.

The vast majority of patients presenting with a hypertensive emergency to an emergency department (ED) have previously been diagnosed with HTN and have been prescribed antihypertensive agents [21,22]. However, in many of these patients BP control prior to presentation was inadequate [22]. The lack of a primary care physician as well as the failure to adhere to prescribed antihypertensive regimens has been associated with the development of a hypertensive emergency [21,23]. In the prospective study by Saguner *et al.* [15], female sex, high grades of obesity, coronary artery disease and nonadherence to medications were associated with hypertensive crisis. In both major metropolitan areas and smaller communities, illicit drug use has been reported to be a major risk factor for the development of hypertensive emergencies [23].

## Pathophysiology

Acute severe HTN can develop *de novo* or can complicate underlying essential or secondary HTN. In white patients, essential HTN accounts for 20–30% of hypertensive emergencies. In African–Americans, however, essential HTN is the predominant cause accounting for approximately 80% of all hypertensive emergencies [24,25]. Genetic factors may increase the likelihood of developing a hypertensive emergency. The DD genotype of the angiotensin-converting enzyme (ACE) gene has been found to be associated with an increased risk of developing a hypertensive emergency [26].

The factors leading to the severe and rapid elevation of BP in patients with hypertensive crises are poorly understood. The rapidity of onset suggests a triggering factor superimposed on preexisting HTN. Hypertensive crises are thought to be initiated by an abrupt increase in systemic vascular resistance likely related to humoral vasoconstrictors [27,28]. The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased permeability, activation of the coagulation cascade and platelets and deposition of fibrin. With severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue [27,28].

This process results in ischemia and the release of additional vasoactive mediators generating a vicious cycle of on-going injury. The renin–angiotensin system is often activated leading to further vasoconstriction and the production of proinflammatory cytokines such as interleukin-6 (IL-6) [29,30]. Furthermore, NADPH oxidase activity increases and generates reactive oxygen species [31]. The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency.

Patients with a hypertensive crisis frequently have a thrombotic microangiopathy with severe microvascular abnormalities resulting in renal or cerebral dysfunction [32]. This microangiopathy is characterized by endothelial dysfunction, platelet activation and increased thrombin generation [32]. Van den Born *et al.* [33••,34] demonstrated increased levels of von Willebrand factor (VWF), VWF propeptide, prothrombin fragment 1R2 (F1R2) and plasmin–antiplasmin (PAP) complexes with reduced levels of ADAMTS13 in patients with a hypertensive crisis (with retinopathy) compared with normotensive controls ($P$ values $<0.01$). Recent data suggest that endothelial dysfunction may persist for years after a hypertensive emergency. Shantsila *et al.* [35] demonstrated the presence of significant macrovascular and microvascular dysfunction (both endothelial dependent and endothelial independent) in patients previously diagnosed with a hypertensive emergency and who had been treated for a mean of 144 months with fairly well controlled BP.

## Clinical presentation

The clinical manifestations of hypertensive emergency are directly related to the particular end-organ dysfunction that has occurred. The signs and symptoms vary from patient to patient. In the STAT registry, the most common presenting symptoms included shortness of breath (29%), chest pain (26%), headache (23%), altered mental status (20%) and focal neurologic deficit (11%) [20]. Microangiopathic hemolysis has been reported in up to 27% of patients presenting with a hypertensive crisis [32]. It is important to make this diagnosis as it is usually associated with reversible renal insufficiency. No particular BP threshold has been associated with the development of a hypertensive emergency. However, organ dysfunction is uncommon with a DBP less than 130 mmHg (except in children and pregnancy) [36]. The absolute level of BP may not be as important as the rate of increase [37–39]. For example, in patients with long-standing hypertension, SBP of 200 mmHg or a DBP up to 150 mmHg may be well tolerated without the development of hypertensive encephalopathy, whereas in children and pregnant women encephalopathy may develop with a DBP of only 100 mmHg [40]. In the STAT registry, the qualifying mean SBP was 200 (IQR 186–220) mmHg and the median DBP 110 (IQR 93–123) mmHg [20].

### Initial evaluation

Patients with hypertensive emergency usually present for evaluation as a result of a new symptom complex related to their elevated BP. Patient triage and physician evaluation should proceed expeditiously to prevent ongoing end-organ damage. A focused medical history that includes the use of any prescribed and over-the-counter medications should be obtained. If the patient is known to have HTN, their hypertensive history, previous control, current antihypertensive medications with dosing and compliance should be obtained. Inquiry into the use of recreational drugs (amphetamines, cocaine and phencyclidine) or monoamine oxidase inhibitors should be made. The physician should confirm the BP in both arms using an appropriate size BP cuff. The appropriate size cuff is particularly important as the use of a cuff too small for the arm size has been shown to artificially elevate BP readings in obese patients [41,42].

The physical examination should attempt to identify the evidence of end-organ damage. Headache, visual disturbance and altered level of consciousness are the usual manifestations of hypertensive encephalopathy [37,43]. Focal neurological findings, especially lateralizing signs, are uncommon in hypertensive encephalopathy but more suggestive of a cerebrovascular accident. Subarachnoid hemorrhage should be considered in patients with a sudden onset of a severe headache. The ocular exam may show evidence of advanced retinopathy with arteriolar changes, exudates, hemorrhages or papilledema assisting in the identification of hypertensive encephalopathy. It is essential to perform a funduscopic examination in all patients with hypertensive emergencies as the presence of an advanced retinopathy is closely associated with the presence of widespread microvascular dysfunction with renal injury [33••]. Remarkably, in the STAT registry a funduscopic examination was documented in only 13% of patients [20]. Cardiac evaluation should aim to identify angina or myocardial infarction with the focus on clarifying any symptoms such as dyspnea, cough or fatigue that may be overlooked [10,44]. Aortic dissection should always be considered in patients with chest pain. On the basis of this evaluation, the clinician should be able to distinguish between hypertensive emergency and urgency and to formulate the subsequent plan for further diagnostic tests and treatment.

Initial objective evaluation should include a metabolic panel to assess electrolytes, creatinine and blood urea nitrogen, a complete blood count with peripheral smear and lactate dehydrogenase (LDH), a urinalysis to look for proteinuria or microscopic hematuria and an electrocardiogram to assess for cardiac ischemia [14]. Microangiopathic hemolysis is diagnosed by the presence of a low platelet count ($<150 \times 10^9$/l) together with either an elevated LDH (>220 U/l) or the presence of schistocytes [32]. Supportive radiographic studies such as a chest radiograph in a patient with cardiopulmonary symptoms or a head computed tomography (CT) scan in a patient with neurologic symptoms should be obtained in the appropriate clinical scenario. If the physical examination or clinical picture is consistent with aortic dissection (severe chest pain, unequal pulses and widened mediastinum), a contrast CT scan or magnetic resonance image of the chest should be obtained promptly to rule out aortic dissection. Although transesophageal echocardiography has excellent sensitivity and specificity for aortic dissection, this study should not be performed until adequate blood control has been achieved. In patients presenting with pulmonary edema, it is important to obtain an urgent echocardiogram to distinguish between diastolic dysfunction, systolic dysfunction or mitral regurgitation [45]. Many patients, particularly the elderly, obese and/or diabetic patients have a normal ejection fraction; in such patients, heart failure is due to isolated diastolic dysfunction [45]. The management of these patients differs from those patients with predominant systolic dysfunction and those with transient mitral regurgitation (see Table 1).

### Initial management of blood pressure

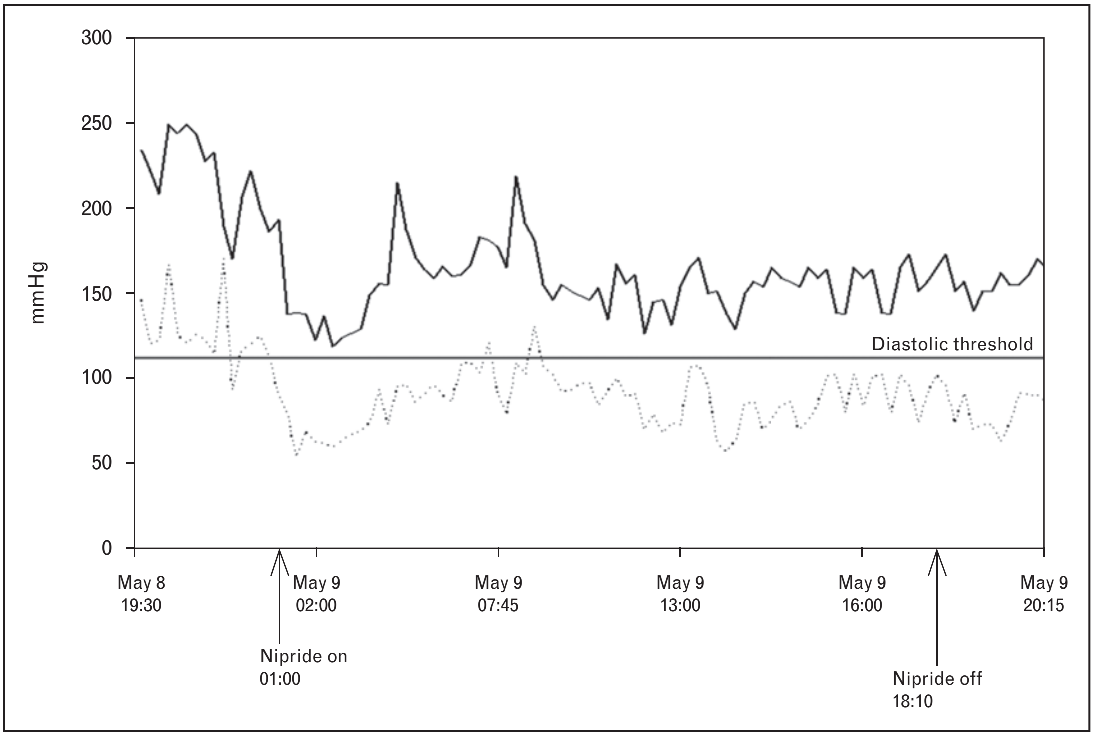
The majority of patients in whom severe HTN (SBP >160 mmHg, DBP >110 mmHg) is identified on initial evaluation will have no evidence of end-organ damage and thus have hypertensive urgency. As no acute end-organ damage is present, these patients may present for evaluation of another complaint and the elevated BP may represent an acute recognition of chronic HTN. In these patients, utilizing oral medications to lower the BP gradually over 24–48 h is the best approach to management [11,46,47]. Rapid reduction of BP may be associated with significant morbidity in hypertensive urgency due to a rightward shift in the pressure/flow auto-regulatory curve in critical arterial beds (cerebral, coronary and renal) [48]. Rapid correction of severely elevated BP below the autoregulatory range of these vascular beds can result in marked reduction in perfusion causing ischemia and infarction [38,49–51]. Therefore, although the BP must be reduced in these patients, it must be lowered in a slow and controlled fashion to prevent organ hypoperfusion.

Altered autoregulation is present in patients with hypertensive emergency and as end-organ damage is already present, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury. Therefore, patients with a hypertensive emergency are best managed with a continuous infusion of a short-acting, titratable antihypertensive agent. Because of unpredictable pharmacodynamics, the sublingual and intramuscular administration should be avoided. Patients with a hypertensive emergency should be managed in an intensive care unit with close monitoring. For those patients with the most severe clinical manifestations or labile BP, intra-arterial BP monitoring may be prudent. There are a variety of rapid-acting intravenous agents that are available for use in patients with hypertensive emergency and the agent of choice depends on which manifestation of end-organ damage is present and the available monitored setting (see Table 1). As mentioned previously, rapid-acting intravenous agents should not be used outside the monitored intensive care unit setting to prevent precipitous falls of BP which may have significant morbidity or mortality (see Fig. 1). The immediate goal is to reduce DBP by 15–20% or to about 110 mmHg over a period of 30–60 min. In aortic dissection, this goal

**Table 1 Recommended antihypertensive agents for hypertensive crises**

| Condition | Preferred antihypertensive agent |
|---|---|
| Acute pulmonary edema – systolic dysfunction | Nicardipine or clevidipine in combination with nitroglycerin and a loop diuretic |
| Acute pulmonary edema – diastolic dysfunction | Esmolol, metoprolol, labetalol or verapamil in combination with low-dose nitroglycerin and a loop diuretic |
| Acute myocardial ischemia | Labetalol or esmolol in combination with nitroglycerin |
| Hypertensive encephalopathy | Nicardipine, clevidipine or labetalol |
| Acute aortic dissection | Labetalol or combination of nicardipine/clevidipine and esmolol or combination of nitroprusside with either esmolol or intravenous metoprolol |
| Preeclampsia, eclampsia (SBP >150 mmHg) | Labetalol or nicardipine |
| Acute renal failure/microangiopathic anemia | Nicardipine, clevidipine or fenoldopam |
| Sympathetic crisis/cocaine overdose | Verapamil, diltiazem, nicardipine or clevidipine in combination with benzodiazepine |
| Acute postoperative hypertension | Esmolol, clevidipine, nicardipine or labetalol |
| Ischemic stroke (SBP >180–200 mmHg) | Nicardipine, clevidipine or labetalol |
| Hemorrhagic stroke (SBP >140–160 mmHg) | Nicardipine, clevidipine or labetalol |

**Figure 1 A 59-year-old man presenting to the emergency department complaining of nausea, vomiting, dizziness, light headedness and blurry vision**

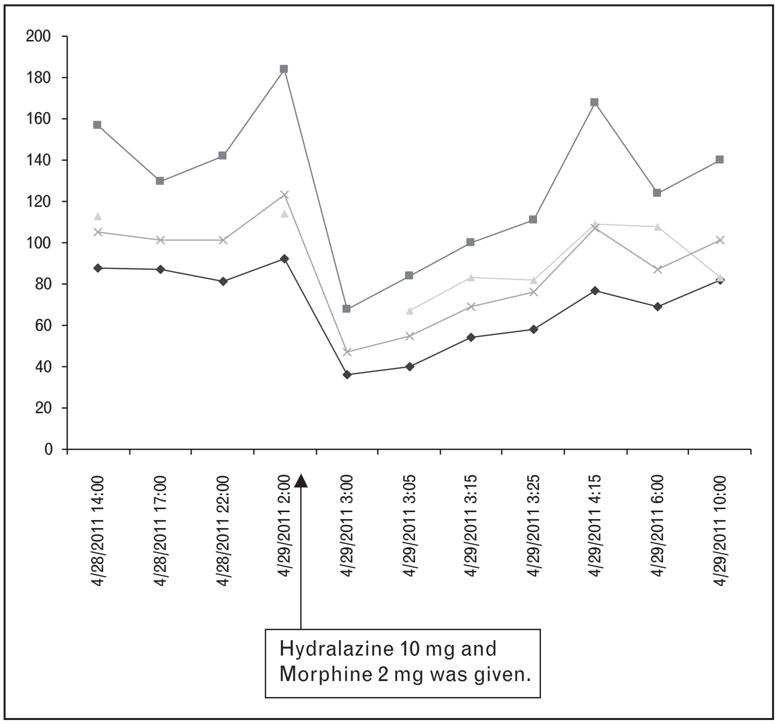



His past medical history included congestive heart failure, type II diabetes, renal dysfunction and hypertension. His blood pressure on arrival in the ED was recorded as 233/146 mmHg. The patient was treated with a 'nitroprusside infusion at 0.5 μg/kg per min titrated to keep SBP less than 190 mmHg' and 80 mg intravenous furosemide. The patient's blood pressure during his stay in the ED is depicted. The patient subsequently suffered a massive stroke, myocardial infarction and acute renal failure and ultimately died. ED, emergency department. ———, SBP; ·········, DBP.

should be achieved within 5–10 min. Once there is stable BP control with intravenous agent(s) and end-organ damage has ceased, oral therapy can be initiated as the intravenous agent(s) is slowly titrated down. An important consideration prior to initiating intravenous therapy is to assess the patient's volume status. Because of pressure natriuresis, patients with hypertensive emergencies may be volume depleted and restoration of intravascular volume with intravenous saline will serve to restore organ perfusion and prevent a precipitous fall in BP when antihypertensive regimens are initiated. Diuretics and intravenous nitroglycerin should be avoided except in patients with pulmonary edema and/or acute coronary syndromes.

Although the indications for parenteral antihypertensive agents and the BP goals (targets) for the management of hypertensive crises have been well established and widely published [36,52–54], our observational experience and published data (supported by a review of the legal literature) suggest that most patients are inappropriately managed (see Fig. 1). In the STAT registry, only 15% of patients were administered a continuous infusion of an intravenous antihypertensive agent as first line therapy [55••]. It is noteworthy that 64% of patients in the STAT registry required multiple drugs for BP control. In an analysis of 47 patients with hypertensive emergencies, Brooks *et al.* [56] reported that only 32% of patients were appropriately treated during the 2-h acute-phase treatment period; 57% were excessively treated (too low a BP) and 11% had treatment failure. At 6 h, only 13% had been appropriately treated. In this study, one or more treatment-related adverse events occurred in 94% of patients. It should be noted that an excessive reduction of BP is more likely to occur with nitroprusside, hydralazine, nitroglycerine and nicardipine and less likely with clevidipine, esmolol or labetalol [55••,56,57]. Sublingual nifedipine and intravenous hydralazine may cause profound hypotension with resulting multiorgan infarction; therefore, these agents have no role in the treatment of hypertensive emergencies. An even more pervasive problem is the 'treatment' of asymptomatic patients (hypertensive urgencies) with intravenous antihypertensive agents (particularly hydralazine) with consequent poor outcomes (see Fig. 2). Weder and Erickson [58••] reviewed the hospital records of 29 545 patients hospitalized to a prestigious tertiary care facility during a 1-year period. The authors

**Figure 2 A 66-year-old woman admitted for hyponatremia**




She complained of nausea and vomiting the night before her arrival to the emergency department. Her oral blood pressure (BP) medications were held as she could not tolerate anything orally. She was ordered hydralazine 10 mg intravenously every 6 h as need for SBP greater than 180 mmHg and labetalol 10 mg intravenously every 6 h as needed for SBP greater than 180 mmHg. Her BP was 184/92 mmHg at 2 am, so she was treated with 10 mg of hydralazine at 2:28 am and morphine 2 mg intravenously at 2:35 am. Her BP dropped to 68/36 mmHg at 3 am. A medical response team alert was called. She was given 1 l bolus of normal saline. Her BP remained labile until 6 am. She recovered and was restarted on her home beta-blocker at 8 am. —■—, SBP; —◆—, DBP; —▲—, heart rate; —×—, mean arterial pressure.

identified 2189 patients (7.4% of all patients) for whom 7242 orders were written for hydralazine as needed (10–20 mg per dose) and 5915 for labetalol as needed (10–20 mg per dose); 60% of patients received one or more doses of the prescribed agent. Although the authors were unable to perform severity-adjusted outcomes, the patients who received these medications had a significantly longer length of hospital stay ($P < 0.001$). This practice is potentially very dangerous. Intravenous antihypertensive agents should 'only' be administered to patients with a hypertensive emergency and then only in a closely monitored environment.

## Preferred pharmacological agents used in the treatment of hypertensive emergencies

The agent of choice for the treatment of a hypertensive emergency will depend upon the patient's clinical presentation (see Table 1). The preferred agents include nicardipine, clevidipine, labetalol and esmolol. Only a single head-to-head study has been performed comparing these agents. Peacock *et al.* [59••] performed a randomized ($n = 226$), comparative, effectiveness trial evaluating the use of nicardipine and labetalol in the ED management of acute hypertension. In this study, patients receiving nicardipine were more likely to have their BP controlled, defined as being within the physicians prospectively defined target range at 30 min, than patients treated with labetalol (91.7 vs. 82.5%, $P = 0.39$; OR 2.73, $P = 0.028$). Lowering the BP below target range occurred in 12.7% of nicardipine patients and 11.2% of labetalol patients. The results of this study are supported by data from the STAT registry in which nicardipine was associated with fewer treatment failures than labetalol [20].

Fenoldopam, phentolamine and trimethaphan camsylate are less commonly used today; however, they may be useful in particular situations. Sodium nitroprusside is a very potent antihypertensive agent that may result in a significant and uncontrolled fall in BP (see Fig. 1). Sodium nitroprusside decreases cerebral blood flow while increasing intracranial pressure, effects that are particularly disadvantageous in patients with hypertensive encephalopathy or following a cerebrovascular accident [60–63]. In patients with coronary artery disease, sodium nitroprusside has been demonstrated to cause coronary steal which increases the mortality of patients with acute myocardial infarction [64,65]. In addition, sodium nitroprusside is associated with clinical cyanide toxicity even at recommended rates of infusion. In the ECLIPSE trials (hypertensive management of cardiac surgery patients), sodium nitroprusside was associated with a significantly higher perioperative mortality when compared to clevidipine [66]. Sodium nitroprusside is a drug of historical interest and should rarely if ever be used in this millennium [52]! Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies [67–73]. Sudden uncontrolled and severe reductions in BP following the administration of nifedipine with cerebral, renal and myocardial infarction and death have been reported [52]. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a benefit, the use of nifedipine capsules for hypertensive emergencies and 'pseudo-emergencies' should be abandoned [74].

Clonidine and ACE inhibitors are long acting and poorly titratable; however, these agents are particularly useful in the management of hypertensive urgencies [70,75–78]. ACE inhibitors are contraindicated in pregnancy [76,79]. Clonidine causes sedation at high doses. When it is withdrawn abruptly, patients can experience rebound HTN. Nitroglycerin is a potent venodilator and only at high doses affects arterial tone [80]. It causes hypotension and reflex tachycardia which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces BP by reducing preload and cardiac output which are undesirable effects in patients with compromised cerebral and renal perfusion. Low-dose ($\leq$60 mg/min) nitroglycerin may, however, be used as an adjunct to intravenous antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.

Hydralazine is a direct acting vasodilator. Following intramuscular or intravenous administration, there is an initial latent period of 5–15 min followed by a progressive and often precipitous fall in BP that can last up to 12 h [81,82]. Although hydralazine's circulating half-life is only about 3 h, the half-time of its effect on BP is about 10 h [83–86]. Because of hydralazine's prolonged and unpredictable antihypertensive effects and the inability to effectively titrate its hypotensive effect, hydralazine is best avoided in the management of hypertensive crises. In the STAT registry, it is noteworthy that nitroglycerin and hydralazine were the initial antihypertensive agents used in 15% of patients each [20].

Volume depletion is common in patients with hypertensive emergencies and the administration of a diuretic together with an antihypertensive agent can lead to a precipitous drop in BP. Diuretics should be avoided unless specifically indicated for volume overload as occurs in renal parenchymal disease or coexisting pulmonary edema. The recommended intravenous antihypertensive agents are reviewed briefly below. Drug dosages and a summary of the kinetics and adverse effects of commonly used intravenous antihypertensive agents are provided in Table 2.

### Nicardipine

Nicardipine is a second-generation dihydropyridine calcium-channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activity. The onset of action of intravenous nicardipine is between 5 and 15 min with a clinical offset of activity (defined as a 10 mmHg increase in SBP or DBP after stopping infusion) within 30 min [87]. Nicardipine's dosage is independent of the patient's weight. Its initial infusion rate is 5 mg/h, increasing by 2.5 mg/h every 5 min to a maximum of 15 mg/h until the desired BP reduction is achieved [36]. A useful therapeutic benefit of nicardipine is that the agent has been demonstrated to increase both stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance [88–92]. This property is useful in patients with coronary artery disease and systolic heart failure. In addition, nicardipine has been shown to reduce cerebral ischemia [88].

### Clevidipine

Clevidipine is a third-generation dihydropyridine calcium-channel blocker that has been developed for use in clinical settings in which tight BP control is crucial [93]. Clevidipine acts by selectively inhibiting extracellular calcium influx through the L-type channel, relaxing smooth muscle of small arteries and reducing peripheral vascular resistance [94]. Stroke volume and cardiac output usually increase. Clevidipine has a half-life of approximately 1 min with a rapid onset and offset, allowing for responsive titration and a decreased risk of overshoot hypotension [95,96]. Additionally, because clevidipine undergoes metabolism by ubiquitous plasma esterases, its elimination is independent of the liver and kidney [95,96]. Clevidipine has been shown to protect against ischemia/reperfusion injury in an animal model of myocardial ischemia and to maintain renal function and splanchnic blood flow [97–99]. Clevidipine is insoluble in water and formulated as a 20% phospholipid emulsion for injection. The recommended starting dose of clevidipine is 1–2 mg/h; the dose is then titrated by doubling at 90-s intervals to a maximum infusion rate of 16 mg/h to achieve a desired goal BP. To minimize the risk of infection, the manufacturer recommends discarding any unused portion of the drug within 4 h of puncturing the vial. Furthermore, because of the lipid load patients should not receive more than 1000 ml

**Table 2 Intravenous antihypertensive medications**

| | Medications | Dosage | Onset | Duration | Adverse effects | Pearls |
|---|---|---|---|---|---|---|
| Beta-blockers | Esmolol | *Bolus*: 500 μ/kg<br>*Continuous*: 25–300 μg/kg per min<br>*Titration*: Increase by 50 μg/kg per min every 4 min | 60 s | 10–20 min | Bradycardia | Bolus with every rate increase<br>Premix bags |
| | Labetalol | Bolus: 10–20 mg, double dose at 10 min intervals to max of 80 mg<br>Continuous: 2–10 mg/min<br>*Titration*: Increase by 1 mg/min every 10 min | 2–5 min | 2–6 h | Bradycardia | Intravenous β to alpha ratio is 7 : 1 |
| | Metoprolol | *Bolus*: 2.5–20 mg | 20 min | 3–4 h | Bradycardia | |
| Calcium channel blockers | Clevidipine | *Continuous*: 1–21 mg/h (maximum because of lipid restriction)<br>*Titration*: Double rate every 90 s until close to goal, then increase rate 5–10 min | 2–4 min | 5–15 min | Reflex tachycardia<br>Acute renal failure | Premix bottles<br>Intralipid vehicle provides 2 kcal/ml |
| | Diltiazem | *Bolus*: 0.25–0.35 mg/kg<br>*Continuous*: 5–20 mg/h | 1–3 min | 1–3 h | Bradycardia | Initial bolus recommended |
| | Nicardipine | *Continuous*: 2.5–15 mg/h<br>*Titration*: Increase by 2.5 mg/h every 5–15 min | 5–15 min | 4 –6 h | Tachycardia<br>Local phlebitis | Premix bags |
| | Verapamil | Bolus: 0.075–0.15 mg/kg | 3–5 min | 0.5–6 h | Bradycardia | |
| Vasodilators | Enalaprilat | Bolus: 1.25–5 mg every 6 h<br>Give over 5 min | 0.5–4 h | 6 h | Variable response | Avoid in renal failure |
| | Fenoldopam | Continuous: 0.01–1.6 μg/kg per min<br>*Titration*: Increase by 0.05–0.1 μg/kg per min every 15 min | 5–15 min | 1–4 h | Reflex tachycardia<br>Increase in serum creatinine | Caution in glaucoma |
| | Hydralazine | *Bolus*: 2.5–5 mg | 5–15 min | 3–10 h, may be prolonged | Drug-induced lupus<br>Reflex tachycardia | Unpredictable BP-lowering effects |
| | Nitroglycerin | *Continuous*: 10–200 μg/min<br>*Titration*: Increase by 5–10 μg/min every 5–10 min | 2–5 min | 10–20 min | Tachyphylaxis<br>Reflex tachycardia | Variable response to dosage changes<br>Premix bottles |
| | Sodium nitroprusside | *Continuous*: 1–4 (?10) μg/kg per min<br>*Titration*: Increase by 0.25–0.5 μg/kg per min every 2–3 min | 3 s | 1–2 min | Tachyphylaxis<br>Muscle twitching | Avoid in renal failure |

(2000 kcal per day) of clevidipine per 24-h period (equivalent to average infusion rate of 21 mg/h).

The safety and efficacy of clevidipine was assessed in an open-labeled, single-arm study (VELOCITY) of 126 patients presenting to the emergency department or ICU with a hypertensive crisis, 81% of whom had acute end-organ damage [57]. Individual BP targets were determined for each patient. Within 30 min of starting clevidipine, 89% of patients achieved target range; the median time to target range was 10.9 min. The mean infusion rate was 5.7 mg/h. The SBP decreased below the prespecified target range in only two patients (1.6%). In addition, the safety and efficacy of clevidipine in the management of postoperative hypertension has been reported in a number of large clinical trials [66,100,101].

### Labetalol

Labetalol is a combined selective alpha-1 and nonselective beta-adrenergic receptor blocker with an alpha-to-beta-blocking ratio of 1 : 7 [102]. Labetalol is metabolized by the liver to form an inactive glucuronide conjugate [103]. The hypotensive effect of intravenous labetalol begins within 2–5 min after administration, reaching a peak at 5–15 min, and lasting for about 2–6 h [103,104]. Because of its beta-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure beta-adrenergic blocking agents which decrease cardiac output, labetalol maintains cardiac output [105]. Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal and coronary blood flow are maintained [105–108]. This agent has been used in the setting of pregnancy-induced hypertensive crises as little placental transfer occurs mainly because of negligible lipid solubility [105]. Labetalol may be given as loading dose of 20 mg, followed by repeated incremental doses of 20–80 mg given at 10-min intervals until the desired BP is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1–2 mg/min and titrating up until the desired hypotensive effect is achieved. Bolus injections of 1–2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided [109].

### Esmolol

Esmolol is an ultra-short-acting, cardioselective, beta-adrenergic, blocking agent [110–112]. The onset of action of this agent is within 60 s with a duration of action of 10–20 min [110–112]. Esmolol metabolizes via rapid hydrolysis of ester linkages by red blood cell esterases and is not dependent upon renal or hepatic function. Because of its pharmacokinetic properties, some authors consider it an 'ideal beta-adrenergic blocker' for use in critically ill patients [36]. This agent can only be given as an infusion because of its short duration of action. Esmolol is particularly useful in severe postoperative hypertension [113–119]. Esmolol is a suitable agent in situations in which the cardiac output, heart rate and BP are increased. Esmolol has proven to be well tolerated in patients with acute myocardial infarction, even those who have relative contraindications to beta-blockers [120]. Typically, the drug is given as a 0.5–1 mg/kg loading dose over 1 min, followed by an infusion starting at 50 μg/kg per min and increasing up to 300 μg/kg per min as necessary. Prior to any dose upward titration, a bolus must be given because of its extremely short half-life.

## Conclusion

Patients with hypertensive emergencies require the immediate reduction of the elevated BP to prevent and arrest progressive end-organ damage. The best clinical setting to achieve this BP control is in the intensive care unit with the use of titratable intravenous hypotensive agents. There are several antihypertensive agents available including nicardipine, clevidipine, labetalol and esmolol. The appropriate therapeutic approach in each patient will depend upon the clinical presentation of the patient. Agents such as nifedipine and hydralazine should be abandoned as these agents are associated with significant toxicities and/or side-effect profile. Patients with hypertensive urgencies require treatment with oral antihypertensive agents; intravenous antihypertensive agents (particularly on an as needed basis) should be avoided in these patients.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 667–668).

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