

# Evaluation and management of hypertensive emergency

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## ABSTRACT

Hypertensive emergencies cause substantial morbidity and mortality, particularly when acute organ injury is present. Careful and effective strategies to reduce blood pressure and diminish the effects of pressure-mediated injury are essential. While the selection of specific antihypertensive medications varies little across different forms of hypertensive emergencies, the intensity of blood pressure reduction to the target pressure differs substantially. Treatment hinges on balancing the positive effects of lowering blood pressure with the potential for negative effects of organ hypoperfusion in patients with altered autoregulatory mechanisms. When patients do not have acute organ injury in addition to severe hypertension, they benefit from a conservative, outpatient approach to blood pressure management. In all cases, long term control of blood pressure is paramount to prevent recurrent hypertensive emergencies and improve overall prognosis. This review discusses the current evidence and guidelines on the evaluation and management of hypertensive emergency.

## Introduction

Hypertensive emergencies are defined by accelerated and severe elevations of blood pressure associated with acute organ injury and have high morbidity. While no uniform threshold exists, blood pressure elevations typically exceed 180 mmHg systolic and/or 110 mmHg diastolic. This review is primarily for clinicians providing care in the hospital and emergency department, but we also provide information for those in the ambulatory setting who see patients with severe elevations in blood pressure. We provide a contemporary overview of the epidemiology, clinical diagnostics, and treatment of adults with hypertensive emergency. Hypertensive disorders of pregnancy, for which a recent state of the art review was published,<sup>1</sup> are not covered in this review. We emphasize the latest evidence on evaluation and management strategies and point to gaps in the literature on the topic.

## Sources and selection criteria

We searched Medline, Embase, and Google Scholar databases for studies published between November 2008 and October 2023 for synonyms of hypertensive emergency and related disorders, including “malignant hypertension,” “hypertensive crisis,” “hypertensive urgency,” “accelerated hypertension,” and hypertensive encephalopathy.” We focused on observational and interventional studies and searched for randomized controlled trials relevant to intracerebral hemorrhage, aortic

dissection, posterior reversible encephalopathy, and hypertensive encephalopathy. We prioritized studies based on the quality of study design, with preference to randomized controlled trials, relevance to the topic, and more recent publication dates. When original research was lacking, we also assessed relevant professional guidelines. While attuned to the relevant literature, we did not design this manuscript as a systematic review. Patients with hypertensive emergency or suspected hypertensive emergency participated in informal interviews with the writing team to inform the clinical perspective within the manuscript.

## Epidemiology

Hypertension affects nearly 1.3 billion people worldwide, of whom as few as 20% have adequate control.<sup>2</sup> In the ambulatory and hospital settings, it is common to evaluate patients with hypertensive crisis, yet the diagnosis of hypertensive emergency is rare. In a cohort of over 2 million patient office visits across an integrated health system, 4.6% of patients had blood pressure measurements >180/110 mmHg.<sup>3</sup> Based on a nationwide inpatient hospital sample in the United States, estimated frequency of hospitalizations with a hypertensive emergency was 101/100 000 in the year 2000, with a modest increase to 111/100 000 in 2007.<sup>4</sup> Nationwide United States emergency department data shows that approximately 0.6% (618/100 000) of emergency

department visits had a diagnosis of hypertensive emergency in 2013.<sup>5</sup>

Men account for a modestly higher proportion of cases of hypertensive emergency than women (52.5% v 47.5%) and have a lower mean age on presentation (55 years v 62 years).<sup>6</sup> Black patients account for the highest proportion of admissions for hypertensive emergency (42.6%) compared with white (40.1%) or Hispanic (11.3%) patients. The reasons for these disparities are complex and are likely linked to negative social determinants of health (SDoH) rather than racial factors alone.<sup>7</sup>

### Risk factors for hypertensive crisis

The risk factors for hypertensive crisis include common factors associated with cardiovascular disease. These include chronic kidney disease, renovascular hypertension, coronary artery disease, heart failure, stroke, alcohol use, and recreational drug use.<sup>8</sup> Furthermore, hypertensive emergencies are associated with comorbid diabetes, hyperlipidemia, and chronic kidney disease. Rare conditions such as pheochromocytoma or inflammatory vascular disease can also lead to hypertensive crisis. Medication non-adherence, lack of medical insurance, and negative SDoH can result in more emergency department visits for severe hypertension; however, there is less consistent evidence that they are linked to a higher risk for true hypertensive emergencies in such patients.<sup>9 10</sup>

A recent review also characterized organ damage among hypertensive emergencies. While hypertension emergency accounted for only 0.5% of emergency department visits, roughly 36% of patients with severely elevated blood pressure were diagnosed with hypertensive emergencies. Ischemic stroke (28.1%), heart failure/pulmonary edema (24.1%), hemorrhagic stroke (14.6%), acute coronary syndrome (10.8%), renal failure (8%), subarachnoid hemorrhage (6.9%), encephalopathy (6.1%), and aortic dissection (1.8%) occurred in descending prevalence.<sup>11</sup> In-hospital mortality remained quite high among all patients (9.9%).

### Classification of hypertensive emergency

The terminology around hypertensive emergencies (table 1) suffers from inconsistent and sometimes misleading language. Hypertensive emergencies are defined as having evidence of new or substantially worsening organ injury and commonly occur with blood pressure levels above 220/110 mm Hg.<sup>4 12-14</sup> Hypertensive emergencies may occur with lower blood pressures in the setting of an accelerated rise from low baseline blood pressure levels (such as young patients with acute kidney injury). It is important to differentiate hypertensive emergencies from longstanding, poorly controlled, but asymptomatic and clinically stable elevations in blood pressure. It is also key to differentiate this diagnosis from transient (often physiological) reactive elevations in blood pressure, such as can occur with severe white coat effect, pain, anxiety/stress responses, and exaggerated exercise-induced elevations.

Acute end-organ injury occurs primarily in the cerebrovascular, cardiovascular, ophthalmologic, hematologic, and renal systems.<sup>15 16</sup> Examples include intracerebral hemorrhage, acute heart failure with pulmonary edema, acute kidney injury, and hypertensive encephalopathy. Without evidence of substantial new or worsening organ injury, patients with severely elevated blood pressures, often above 180/110 mm Hg, are classified as having markedly elevated or acute severe hypertension. Even blood pressure values >220/110 mm Hg do not constitute a hypertensive emergency unless new or acute worsening of end-organ injury is present.

Many authors and published guidelines in the past have used the term “hypertensive urgency” to describe patients with severely elevated blood pressure.<sup>17 18</sup> The term “urgency,” however, insinuates that clinicians should urgently treat patients, when doing so has been shown to offer no clinical benefit and can be linked to potential for harm.<sup>3</sup> Authors have also noted that this term has the potential to cause unnecessary anxiety for patients,<sup>19</sup> and recent European Society of Hypertension guidelines point out the ambiguity of this term.<sup>20</sup> The term hypertensive crisis has been

**Table 1 | Terminology used for hypertensive emergencies, definition, and incidence at emergency departments**

| Terminology   | Definition  | Incidence* |
|---|---|------------|
| Severe hypertension, severely or markedly elevated BP       | BP >180/110 mm Hg, acute end-organ injury absent  | 4-6%       |
| Hypertensive emergency:                                     | Acute end-organ injury present due to severe hypertension. Immediate BP lowering is clinically beneficial                                   | 0.6-1.0%   |
| Neurologic  | Examples: hypertensive encephalopathy, intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke <sup>†</sup>                      | —          |
| Cardiovascular  | Examples: acute heart failure, acute myocardial ischemia, <sup>†</sup> aortic dissection  | —          |
| Obstetric   | Examples: pre-eclampsia, eclampsia  | —          |
| Other   | Examples: acute kidney injury, <sup>†</sup> thrombotic microangiopathy, <sup>†</sup> acute moderate to severe hypertensive retinopathy      | —          |
| Acute medical emergency with associated severe hypertension | Acute end-organ injury present. Severe hypertension is not a direct cause of injury, and immediate BP lowering is not clinically beneficial | —          |
| <b>Unclear terminology</b>                                  |   |            |
| Hypertensive urgency  | Often used to indicate severe hypertension without acute organ injury. Assumes an unfounded treatment urgency                               | —          |
| Hypertensive crisis   | Indicates severe hypertension with or without acute organ injury. Assumes an unfounded treatment urgency when acute organ injury is absent  | —          |
| Malignant hypertension                                      | Being redefined as microvascular injury with organ damage in 3 or more target organs  | —          |

BP = blood pressure.

\*Incidence based on emergency department diagnoses.

†Conditions rarely consistent with a hypertensive emergency and more likely to be an acute emergency with associated severe hypertension

used to identify patients with severely elevated blood pressure with or without hypertensive emergency and has also contributed to ambiguity in the literature.<sup>20</sup> Malignant hypertension is a term that reflects the vascular injury that results from loss of usual autoregulation of blood flow. Small arterioles develop fibrinoid necrosis and onion skinning. These findings may be evident clinically when hypertensive retinopathy is evident on exam.<sup>21 22</sup> The “malignant” term originated nearly a century ago when effective antihypertensive medications were not yet available and the prognosis was akin to active malignancy. Malignant hypertension remains problematic and contributes to significant morbidity.<sup>23 24</sup> Recent authors have reconceptualized the diagnosis of malignant hypertension to emphasize microvascular injury and concomitant damage of three or more organs.<sup>23 25 26</sup>

We must acknowledge controversies that stem from a long history of expert opinion informing this field, the tendency to maintain terminologies within subsequent guidelines, and the paucity of high quality randomized controlled trials to inform definitions and care pathways.<sup>27</sup> While acute organ damage is the *sine qua non* of a hypertension emergency, in many scenarios there is a “chicken and egg” conundrum. Acute medical emergencies (such as stroke, aortic dissection, and myocardial ischemia) are often associated with considerable physiological stress and pain, which may secondarily prompt severe elevations in blood pressure. While longstanding hypertension may (or may not) have played a role in the cause of the acute condition, the rapid elevation in blood pressure could be a feed-forward facilitator (that is, a true hypertension emergency) versus an innocent bystander or reactive secondary phenomenon. In the former case emergent

lowering of blood pressure would produce a health benefit, whereas in the latter scenario (such as post-ischemic stroke) it does not.

We propose that another layer of definitions should be considered. A hypertensive emergency should also acknowledge two essential points. First, severe hypertension directly causes or worsens the acute medical condition. Second, evidence supports that immediate lowering of blood pressure intrinsically provides clinical benefit. The quintessential example is hypertensive encephalopathy. Conversely, blood pressure often rises following an acute ischemic stroke and has no direct role in the etiology of the acute event. Immediate blood pressure lowering offers no clinical benefit. Conditions are common in which severe elevations in blood pressure and end-organ injury are present, but immediate lowering is not beneficial and organ injury is not directly caused by the severely elevated blood pressure.

### Pathophysiology

The pathophysiology of hypertension emergency has been poorly studied and is multifactorial in nature. We provide an overview, but a detailed mechanistic analysis is beyond the scope of this review. Uncontrolled hypertension is associated with long term endothelial damage, including oxidative stress and impaired production of nitric oxide.<sup>28</sup> Arteriole thickening and atherosclerosis lead to narrowing and diminished compliance, including in the cerebral circulation (fig 1). An overarching hypothesis related to a final common pathway underlying hypertensive emergency is believed to involve the failure of the autoregulatory mechanism in the vascular bed and an abrupt rise in systemic vascular resistance. This leads to microcirculatory damage, excessive renin-angiotensin system activation and vasoconstriction, pressure natriuresis, and volume depletion which contributes to a feed-forward process and accelerated blood pressure elevations.

Understanding the effects of hypertension on the cerebral circulation is essential in the evaluation and management of hypertensive emergency. The process of cerebral autoregulation maintains constant blood flow across a broad range of systemic arterial pressure. For normotensive patients, the upper threshold of this range is approximately a mean arterial pressure of 150 mmHg.<sup>29 30</sup> However, in patients with uncontrolled hypertension over long periods of time, the cerebral vasculature undergoes pathological remodeling and impaired smooth muscle function that shift this threshold to the right (fig 2).<sup>31</sup> Hence, patients in hypertensive emergency may be well tolerant of mean arterial pressure values well above 150 mmHg.<sup>32</sup>

Due to these adaptations, many patients with acute severe hypertension are at low risk of immediate cerebral injury due to autoregulatory failure and associated end-organ injury. Rather, there exists potential for harm with over-aggressive treatment, such as watershed ischemia and renal injury.<sup>33-36</sup> Rapid lowering of blood pressure has the potential

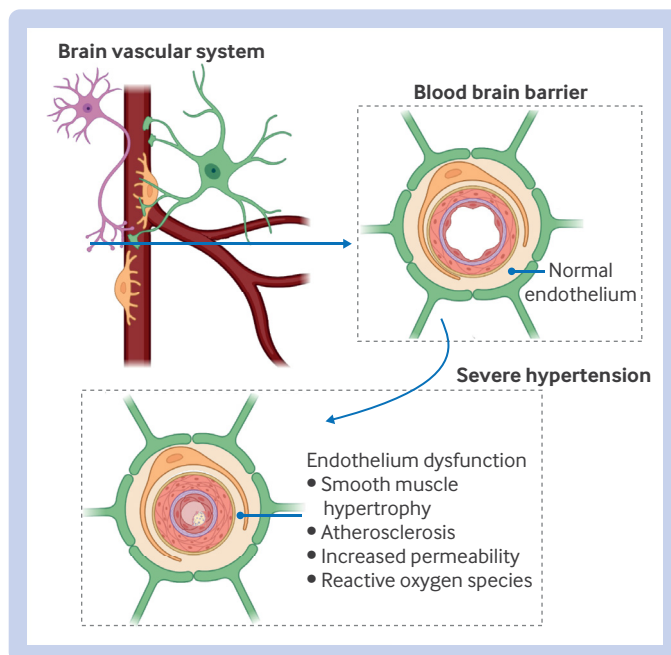


Fig 1 | Neurovascular remodeling due to severe, uncontrolled hypertension

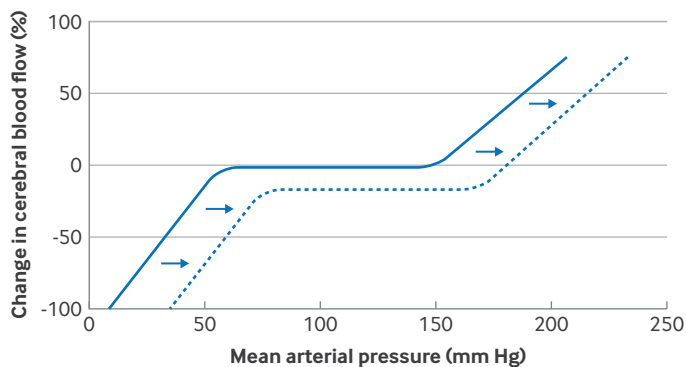


Fig 2 | Shifting of cerebral autoregulatory curve to the right due to chronic, uncontrolled hypertension

to cause adverse cerebrovascular effects, particularly in patients with chronic, uncontrolled hypertension. Over time, these patients reset their cerebral autoregulatory limits and may tolerate rapid blood pressure normalization poorly. Such changes are reversible with treatment, and, over time, patients reset their cerebral autoregulatory curve toward normal levels.

#### Diagnostic evaluation of suspected hypertensive emergency

We focus this discussion on evaluation of key organs affected by hypertensive emergency and appropriate laboratory and imaging testing. The first, but often overlooked step in evaluation is proper blood pressure measurement. Particularly in the emergency department and hospital setting, it is common for measurements to stray from best practice. Remeasurement with an appropriately sized and positioned cuff and ensuring that the patient is seated and relaxed can exclude the need for further evaluation.<sup>37</sup> Furthermore, remeasurement after adequate analgesia for patients with severe pain often ameliorates markedly elevated blood pressure measurements. In conditions where intensive treatment is warranted, such as aortic dissection, invasive arterial blood pressure monitoring allows for continuous measurements. When less intensive treatment is needed, non-invasive and appropriately sized automated cuffs may be adequate for antihypertensive titration.

#### Clinical evaluation

Once appropriate blood pressure measurements confirm severe hypertension that was not specious or reactive to stress or pain, the history taking and physical examination focus on symptoms and findings related to organ injury.<sup>38-41</sup> The clinical history includes previous diagnosis of hypertension, cardiovascular disorders, cardiometabolic disorders, endocrine disorders, pheochromocytoma, and chronic kidney disease. Furthermore, history includes recent alcohol intake (or cessation), sympathomimetic drugs, supplements, and medication adherence.<sup>42</sup> Drugs containing amphetamines, methamphetamine, and cocaine

are common and may precipitate hypertensive emergencies. In females of reproductive age, the history should include current or prior pregnancy related elements.

A focused neurological and ophthalmic history and exam is highly valuable in the evaluation of severe hypertension. Seizures and altered consciousness can be indicative of hypertensive encephalopathy. Although it is a common finding (in nearly 25% of patients with severely elevated blood pressure), headache alone does not indicate the presence of a hypertensive emergency.<sup>39</sup> Focal neurological deficits point to intracerebral hemorrhage or ischemic stroke. Visual symptoms, visual acuity, and fundoscopic exam are also valuable assessments. Fundoscopic exam determines severity of hypertensive retinopathy.<sup>43</sup> Arteriole tortuosity and arteriovenous nicking are indicative of mild hypertensive retinopathy and are chronic findings. New flame hemorrhages, cotton-wool spots, or microaneurysms suggest more acute injury and are consistent with moderate or grade 3 retinopathy. The added finding of papilledema is consistent with severe retinopathy and requires immediate blood pressure lowering.

Cardiovascular symptoms such as chest pain (26%), shortness of breath (29%), palpitation, and claudication are also common in patients with possible hypertensive emergency.<sup>44</sup> Exam can reveal clear signs of acute heart failure and pulmonary edema (jugular venous pulsation, extra heart sounds, pulmonary rales, peripheral edema) or less common findings of vascular pathology such as abdominal bruits or discordant peripheral pulses. Diaphoresis, palpitations, frequent headaches, and autonomic instability could prompt further evaluation for pheochromocytoma.

A hierarchical strategy has been proposed to differentiate a true hypertensive emergency by evaluating for five symptoms: chest pain, dyspnea, headache, visual disturbances, or other neurological symptoms.<sup>45</sup> In a retrospective study the absence of any symptoms ruled out an emergency with a negative predictive value of 99%.<sup>46</sup> Conversely, the presence of any symptom had poor positive predictive value (23%). While further work is needed to improve predictive models, these findings confirm that a true hypertensive emergency is uncommon among asymptomatic individuals even when they present with severe hypertension.

#### Diagnostic testing

##### Laboratory testing

In patients with acute severe hypertension and no symptoms, diagnostic testing can be minimal. In those with symptoms and concern for hypertensive emergencies, clinicians can tune diagnostic testing to specific symptoms and potential associated organ involvement. Most of these patients will require an electrocardiogram, a complete blood count with differential, and a metabolic profile assessing sodium, potassium, creatinine, and estimation of glomerular filtration. The presence of acute kidney injury and



fragmented red blood cells are important markers of hypertensive emergencies. Other laboratory studies can include thyroid function studies, urine analysis for protein, and urine sediment for erythrocytes, leukocytes, and casts.<sup>37 47</sup>

Some experts advocate laboratory evaluation of secondary causes of hypertension, including plasma renin activity, aldosterone, and catecholamines.<sup>42</sup> However, these tests for secondary causes are rarely evaluated in the emergency department setting. Given stimulation of the renin-angiotensin system (that is, secondary hyperaldosteronism), volume depletion, and sympathetic activation that occur in severe hypertension, the evaluation for many secondary causes of hypertension (such as primary aldosteronism, pheochromocytoma) can be confounded.<sup>48-50</sup> While secondary hypertension can contribute to uncontrolled hypertension, the prevalence and contributing role in hypertensive emergency is not well described.<sup>51</sup> With the possible exception of diagnosing key hyperadrenergic states (such as drug induced, pheochromocytoma) that may benefit from unique treatments, it remains unclear if the immediate management course in the emergency setting will be modified. A high index of suspicion to rule out hyperadrenergic states is needed, whereas the evaluation for other secondary causes of hypertension can typically be deferred until the patient is stable.

Circulating biomarkers such as brain natriuretic peptide (BNP) or NT-proBNP and high sensitivity troponin are valuable in evaluation of cardiovascular symptoms, ruling out myocardial damage and heart failure, and provide important prognostic information. Lactate dehydrogenase (LDH), which reflects thrombotic microangiopathy, may also have value in the evaluation of hypertensive emergency. In a small prospective observational study, LDH levels >190 U/L were associated with hypertensive emergency.<sup>52</sup> Further study is needed to determine the accuracy and prognostic value of LDH. High sensitivity troponin values are essential in diagnosing acute myocardial infarction, and details on interpreting these results are discussed below. Studies have also shown high positive predictive value in elevated NT-proBNP for hypertensive emergency.<sup>52 53</sup> Other biomarkers—including C reactive protein, plasminogen activator inhibitor-1, D-dimer, urinary albumin:creatinine ratios, and novel factors related to renal, cerebrovascular, or endothelial damage—have been considered, but their clinical utility in hypertensive emergency is not established.<sup>54</sup>

### *Imaging*

Imaging in patients with potential hypertensive emergencies is tailored to symptoms and suspected organ injury, and often incorporates plain radiography and computed tomography (CT). Head CT imaging is insensitive for the diagnosis of hypertensive encephalopathy and should not be used to rule out this emergency. Rather, non-contrast head

CT in patients with severely elevated blood pressure and altered mental status is critical for determining the presence or absence of intracerebral hemorrhage. In a small number of patients with hypertensive encephalopathy, the non-contrast head CT may reveal vasogenic edema, often in a bi-hemispheric distribution.

Hypertensive encephalopathy remains a clinical diagnosis and does not require imaging findings of vasogenic edema. If available, magnetic resonance imaging (MRI) has greater sensitivity in identifying vasogenic edema and can solidify the diagnosis when uncertainty is present. Vasogenic edema is commonly seen in a parieto-occipital pattern, which is consistent with the radiological classification of posterior reversible encephalopathy syndrome. The vasogenic edema appears as hyperintense lesions in T2-weighted or fluid attenuated inversion recovery (FLAIR) sequences. Brain MRI may also reveal microhemorrhages in about 65% of patients with hypertensive encephalopathy.<sup>55</sup> Brain MRI is also critical in differentiating hypertensive encephalopathy from acute stroke when both diagnoses are being considered.

The role of ultrasonography in the evaluation of cardiovascular hypertensive emergencies is evolving. Echocardiography can be useful for assessing left ventricular hypertrophy, systolic and diastolic dysfunction, atrial dilation, and aortic coarctation. While not sensitive, bedside point of care ultrasonography has good specificity for the diagnosis of acute aortic dissection, particularly when the dissection extends into the abdominal aorta.<sup>56</sup> Lung ultrasonography is an accurate method of diagnosing acute pulmonary edema through detection of B-lines.<sup>57</sup>

Other forms of ultrasonography may be limited in evaluating hypertensive emergencies but can confirm longstanding effects of uncontrolled hypertension on vascular damage. These include carotid ultrasound assessing for stenosis or plaques, renal artery duplex for stenosis, and carotid-femoral pulse wave analysis for arterial stiffness.<sup>37 45 47 58</sup> Similarly, pulse wave analysis devices can provide useful information on subclinical vascular damage by measuring pulse waves and estimating arterial stiffness.<sup>59</sup> In the prospective, observational ERIDANO study, investigators are using this pulse wave analysis to quantify arterial stiffness following an emergency department visit for severely elevated blood pressure.<sup>58</sup>

### **Management**

#### **Severely elevated blood pressure without emergency**

Management decisions depend on the presence or absence of a hypertensive emergency that requires immediate blood pressure lowering (fig 3). Most patients evaluated for hypertensive emergency have a negative work-up for acute organ injury and are diagnosed with acute severe hypertension. They may often be managed as an outpatient. Their risk of

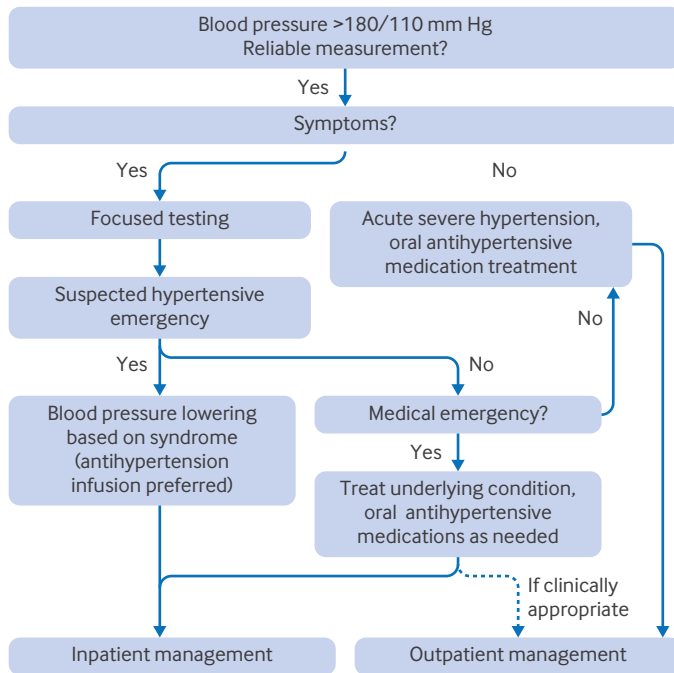


Fig 3 | Overview of evaluation and management strategy for suspected hypertensive emergency

long term cardiovascular disease is substantial, but short term adverse cardiovascular events have not been demonstrated.<sup>3 38</sup> In a large retrospective study of 59 535 patients presenting to outpatient clinics, 4.6% of patient had blood pressure measurements >180/110 mmHg. Most (72.9%) of these patients had a known diagnosis of hypertension, and 58.2% were taking two or more antihypertensives.<sup>3</sup> For these patients, referral to the emergency department and hospital admission were not associated with better outcomes.

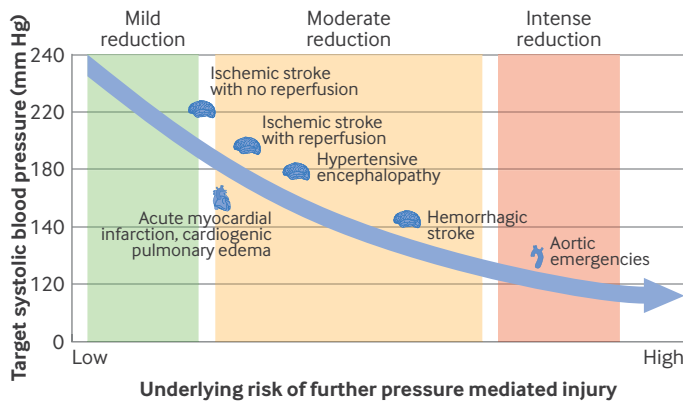
In a case of acute severe hypertension in the emergency department when it is unclear if this is a hypertensive emergency, clinicians may consider a period of observation. In patients thought to be at low risk for hypertensive emergency, a period of quiet resting has been shown as effective as a medication in lowering blood pressure over two hours in a randomized trial.<sup>60</sup> In this trial of 138 patients randomized to rest or treatment with telmisartan, the mean blood pressure reduction at two hours was 32.2 and 32.8 mmHg respectively (non-significant difference,  $P=0.065$ ). Mindfulness combined with slow breathing may also be highly effective.<sup>61</sup> In a trial of 110 patients randomized to usual care versus a mindfulness exercise using pursed-lip breathing and number counting, there was greater mean reduction in systolic blood pressure in the intervention group compared with usual care at 3 hours (difference 9.8 mmHg (95% CI 4.1 to 15.5)).<sup>61</sup> A pilot trial and observational data have shown that anxiolytics lower blood pressure in this scenario as well.<sup>62 63</sup> The pilot trial randomized 36 patients to oral diazepam or captopril and showed a decrease in mean systolic blood pressure from 213 to 170 mmHg

in the diazepam group and from 208 to 181 mmHg in the captopril group.<sup>62</sup> Resumption of outpatient oral antihypertensive medications is appropriate. In patients without known outpatient medications, initiation of an oral antihypertensive medication according to guidelines is reasonable while awaiting additional testing.<sup>17 18</sup> In all patients ultimately discharged to outpatient follow-up, barriers to ongoing antihypertensive management must be addressed. Such barriers may include financial and insurance-based challenges, educational gaps, transportation difficulties, and other social factors. Upwards of 65% of patients have uncontrolled hypertension at six months after an emergency department visit for severe hypertension.<sup>3</sup>

When patients require inpatient hospital admission for diagnoses other than hypertensive emergencies and have acute severe hypertension during their hospital stay, which can occur for a variety of reasons (such as pain, anxiety, poor sleep, excessive fluids), there is significant heterogeneity in management. Strategies range from use of oral medications as needed (such as clonidine, labetalol), to gradual titration of long acting oral antihypertensives, to intensive therapy with intravenous antihypertensive agents. Observational evidence points to harm associated with intensive treatment with intravenous antihypertensives as well as from use of as-needed medications to control blood pressure spikes without a clear indication of hypertensive emergency.<sup>64-66</sup> This practice should be discouraged.

A retrospective study of 66 140 patients hospitalized for non-cardiovascular conditions found that intravenous antihypertensive treatment was associated with more severe adverse outcomes such as acute kidney injury and transfer to intensive care.<sup>64</sup> In this study, approximately 15% of those treated had a systolic blood pressure >180 mmHg. A similar observational study analyzing data from nearly 23 000 hospitalized adults in 10 hospitals within the Cleveland clinic found that those treated for acute hypertension had higher rates of acute kidney injury and myocardial infarction.<sup>65</sup> Lastly, another retrospective review of 2189 patients evaluated the use of intravenous hydralazine and labetalol: only 3% of the patients met clear indications for intravenous therapy, and these patients had longer associated length of hospital stay compared with those not receiving intravenous therapy.<sup>66</sup>

The optimal approach to managing patients with acute severe hypertension in the hospital is gradual and stepwise titration of guideline recommended oral antihypertensive agents. Intravenous treatment is rarely, if ever, indicated. Treating pain, whether postoperative pain or from other causes, often ameliorates severe rises in blood pressure. Efforts to address anxiety or withdrawal states are also indicated.<sup>40</sup> While it is important to treat severely elevated blood pressure when acute end-organ injury is present, many of these patients will continue to have elevated blood pressure as an outpatient and require a coordinated strategy over weeks to months



**Fig 4 | Recommended intensity of blood pressure lowering target relative to the underlying risk of further pressure-mediated injury in hypertensive emergency syndromes**

to progressively control blood pressure and prevent long term complications.<sup>38 67</sup>

#### Management of specific hypertensive emergencies

Guidelines for the management of hypertensive emergency unanimously recommend immediate treatment when organ injury is present. The treatment follows a stepwise pathway, including initial reduction in blood pressure, careful monitoring of the patient's clinical status, and subsequent gradual blood pressure lowering toward normal limits. While broad recommendations are discussed in this section, treatment must be also modified and directed to the underlying cause, patient comorbidities, and special circumstances. Initial blood pressure treatment intensity is generally mild to moderate, avoiding rapid decreases, in most clinical scenarios. Caution must be used in treating blood pressure too rapidly in order to avoid end-organ ischemia in areas with altered vascular autoregulation in cases

of chronic hypertension. Figure 4 demonstrates the intensity of lowering relative to the underlying risk of further pressure-mediated injury based on specific syndromes.

We present an overview of blood pressure management categorised by organ involvement (table 2) and highlight common themes. Obstetric hypertensive emergencies were discussed in a recent state of the art review and not included here.<sup>1</sup> Randomized controlled trial data informing the management of hypertensive emergencies are lacking in all areas outside of ischemic and hemorrhagic stroke. Hence, we present data from randomized trials where applicable, but observational data and expert opinion guide most treatment recommendations. We focus medication recommendations on the existing literature and use of rapidly effective, titratable medications. To this end, we universally recommend intravenous antihypertensive medications and favor continuous infusions for initial management. Two particular medications, intravenous hydralazine and nitroprusside, are not recommended. Hydralazine is inconsistent in its effects and difficult to titrate, and both agents can lead to unexpected, sudden drops in blood pressure beyond intended targets.<sup>66 76</sup>

#### Hypertensive encephalopathy

Hypertensive encephalopathy is defined by alterations in mental status with severely elevated blood pressure beyond a patient's limits for cerebral autoregulation. Symptoms may also include seizures, headache, lethargy, and visual disturbances. Blood pressure is commonly >220/110 mmHg to exceed autoregulatory limits. In young adults or those without a history of chronic hypertension, however, rapid increases in blood pressure even to lower elevated ranges are possible. Concomitant findings can include acute hypertensive retinopathy and microangiopathic hemolytic anemia. While there

**Table 2 | Treatment approaches to hypertensive emergency syndromes**

| Category   | Initial hemodynamic targets   | Agent of choice                           | Alternative                              |
|--|---|---|--|
| Aortic emergencies (aortic dissection)                     | SBP <120 mm Hg<br>HR <60 bpm  | Esmolol and nicardipine                   | Clevidipine<br>Labetalol                 |
| Hemorrhagic stroke <sup>68 69</sup>                        | SBP 140-180 mm Hg<br>If baseline SBP >220 mm Hg, target near 180 mm Hg                                  | Nicardipine                               | Clevidipine<br>Labetalol                 |
| Subarachnoid hemorrhage <sup>70</sup>                      | Gradual reduction if baseline SBP >180 mm Hg  | Nicardipine                               | Clevidipine<br>Labetalol                 |
| Ischemic stroke <sup>71-74</sup>                           | Reperfusion therapy: SBP <185 mm Hg and DBP <110 mm Hg<br>All others: SBP <220 mm Hg and DBP <120 mm Hg | Nicardipine<br>Labetalol                  | Clevidipine                              |
| Myocardial infarction, acute pulmonary edema <sup>75</sup> | MAP reduction by 15-25%   | Nitroglycerin<br>Labetalol<br>Furosemide* | Esmolol<br>Nicardipine<br>Clevidipine    |
| Hypertensive encephalopathy                                | MAP reduction by 20-25%   | Nicardipine                               | Labetalol<br>Clevidipine                 |
| Acute kidney injury  | MAP reduction by 20-25%   | Labetalol<br>Nicardipine                  | Clevidipine                              |
| Pheochromocytoma or adrenergic crisis                      | MAP reduction by 20-25%   | Phentolamine                              | Nicardipine<br>Clevidipine<br>Labetalol† |

Most emergencies lack clinical trial data and are based on expert opinion, but we provide references where such data exist.

BPM = beats per minute; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; \*reperfusion therapy" includes IV thrombolysis or endovascular therapy.

\*Furosemide or budesonide indicated for decongestion and small contribution to blood pressure lowering.

†Labetalol is an option following a blockade with phentolamine.

are characteristic patterns often observed on MRI, the diagnosis remains principally a clinical one and requires exclusion of other acute neurological hypertensive emergencies such as ischemic or hemorrhagic stroke. The patterns most commonly seen on MRI are those seen with posterior reversible encephalopathy syndrome.

The treatment goal in hypertensive encephalopathy is immediate reduction of blood pressure to restore cerebral autoregulation. Current guidelines recommend reduction of the patient's initial mean arterial pressure (MAP) by 20-25% within the first hour of care. There are no high quality studies to provide strict parameters for MAP reduction. First line antihypertensive agents include nicardipine, clevidipine, and labetalol. Given its effectiveness and ease of titration, nicardipine is often preferred.<sup>37-45</sup> After initial lowering of blood pressure, clinicians should maintain the target MAP over the next 2-6 hours to ensure it is well tolerated. In the event that MAP falls beyond the anticipated <25% reduction, fluid resuscitation is indicated. Pressure natriuresis is a consequence of severe arterial hypertension and can lead to intravascular depletion due to increased renal sodium excretion. Once initial blood pressure lowering is tolerated, further gradual reduction toward a blood pressure of 160/110 mm Hg over the next 48 hours is acceptable.<sup>47</sup>

#### *Aortic disease*

In the case of aortic dissection and other acute aortic syndromes, standard practice and societal guidelines dictate immediate afterload reduction with systolic blood pressure <120 mm Hg and impulse control with a heart rate <60 beats per minute. US and European professional guideline recommend  $\beta$  blockade in conjunction with calcium channel blockers as first line therapy.<sup>77-78</sup> Because of its rapid effectiveness and ease of titration, esmolol combined with nicardipine or clevidipine is an excellent first line agent.<sup>79</sup> Nitroprusside used to be a first line antihypertensive agent for afterload reduction in aortic dissection, but it has a less favorable side-effect profile (including reflex tachycardia, coronary steal, and the potential for cyanide toxicity) than newer short acting calcium channel blockers.

Acute aortic emergencies are the only category of hypertensive emergencies for which >25% reduction in mean arterial pressure is indicated. Guidance to treat intensively is based on the immediate risk of dissection extension and mortality. Nevertheless, because many of these patients may have right-shifting of their cerebral autoregulatory limits, risk of cerebral hypoperfusion exists. In a retrospective cohort study that assessed blood pressure lowering in the management of 112 patients with type B aortic dissection, rates of cerebrovascular injury rose substantially with reductions in MAP beyond 25%.<sup>35</sup>

#### *Hemorrhagic stroke and subarachnoid hemorrhage*

Of all hypertensive emergencies, the best evidence base for blood pressure management is for

hemorrhagic and ischemic stroke. For hemorrhagic stroke, immediate reduction of blood pressure is recommended by the International Society of Hypertension and European Society of Cardiology to a goal systolic blood pressure <130 mm Hg.<sup>37-45</sup> Current guidelines by the American Heart Association/American Stroke Association (AHA/ASA) target a goal systolic blood pressure of 140 mm Hg, with the caveat that clinicians consider higher targets if patients present with systolic blood pressure >220 mm Hg.<sup>47</sup> The greater caution in patients with higher presenting blood pressure stems from the concern for right-shifted cerebral autoregulation and risk of hypoperfusion injury with intensive blood pressure reduction.

Major randomized controlled trials assessing blood pressure targets in hemorrhagic stroke include INTERACT-2, ATACH-2, and INTERACT-3.<sup>68-80</sup> The INTERACT-2 trial randomized 2839 patients to a target systolic blood pressure of either 140 mm Hg or 180 mm Hg.<sup>68</sup> The more intensive target was safe but did not significantly reduce the risk of death or major disability compared with the less intensive target (odds ratio with intensive treatment 0.87 (95% confidence interval 0.75 to 1.01)). The ATACH-2 trial similarly randomized 1000 hemorrhagic stroke patients to systolic blood pressure targets of 110-139 mm Hg or 140-179 mm Hg using nicardipine as the primary antihypertensive.<sup>80</sup> It showed no significant difference in the risk of death or disability based on these different blood pressure targets (relative risk 1.04 (95% CI 0.85 to 1.27)).

The recently published INTERACT-3 trial was a pragmatic, cluster randomized trial of 66 140 patients in 121 hospitals in low to middle income countries.<sup>69</sup> It tested whether intensive systolic blood pressure reduction (<140 mm Hg) included in a therapeutic bundle of glucose control, temperature management, and coagulopathy reversal was superior to usual care. Use of this therapeutic bundle was associated with reduced disability and death at six months (odds ratio 0.86 (95% CI 0.76 to 0.97)).

Based on the success of this trial and the demonstrated safety in the earlier trials, we recommend a target systolic blood pressure of 140 mm Hg for most hemorrhagic stroke patients. In those patients who have systolic blood pressure measurements >220 mm Hg, more conservative lowering to <180 mm Hg is reasonable. Short acting calcium channel blockers, including nicardipine and clevidipine, are excellent first line antihypertensive medications. Comparatively, clevidipine and nicardipine achieve similar rates and efficacy of reduction, with nicardipine being more readily available and at lower cost.<sup>71</sup>

Compared with intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage less commonly has accompanying severe elevations in blood pressure. Prior guidelines had recommended targeting systolic blood pressure <160 mm Hg but were based on low quality data. Current AHA/ASA guidelines recommend gradual blood pressure



lowering when systolic blood pressure exceeds 180 mmHg.<sup>81</sup> Similar medication choices are appropriate such as nicardipine.

#### *Ischemic stroke*

In the early management of hypertensive emergency and ischemic stroke, the need for acute reperfusion therapy (thrombolytic and/or endovascular thrombectomy) guides blood pressure targets. In patients with an ischemic stroke who do not receive acute reperfusion therapy, immediate blood pressure lowering is not indicated unless blood pressure exceeds 220/120 mmHg. For these patients, gradual antihypertensive titration over several days is appropriate.

Two large trials in China investigated immediate or delayed treatment of elevated blood pressure in ischemic stroke. The first CATIS trial randomized 4071 patients to blood pressure reduction of 10-25% in the first 24 hours compared with withholding antihypertensive medications.<sup>72</sup> The treatment arm had no difference in rates of death and disability following hospital discharge (odds ratio 1.00 (95% CI 0.88 to 1.14)). The subsequent CATIS-2 trial enrolled 4810 patients with mild to moderate stroke and systolic blood pressure 140-220 mmHg and tested if a 10-20% blood pressure reduction in the first 24 hours followed by gradual reduction to <140 mmHg was superior to permitting higher pressures.<sup>82</sup> Those in the intervention arm compared to a permissive approach had no significant difference in rate of death and disability at day 90 (odds ratio 1.18 (0.98 to 1.41)).

For patients receiving acute reperfusion therapy, international guidelines recommend blood pressure goals of systolic <185 mmHg and diastolic <110 mmHg.<sup>83</sup> Recommended antihypertensive agents include continuous nicardipine or intermittent intravenous labetalol. The AHA/ASA guidelines also recommend maintenance of blood pressure <180/105 mmHg for the first 24 hours after administration of reperfusion therapy.<sup>83</sup>

Blood pressure management for thrombectomy patients has been studied in the past several years. The ENCHANTED2 trial performed in China randomized 821 patients to intensive blood pressure management (systolic blood pressure <120 mmHg) or to a moderate approach (systolic blood pressure 140-180 mmHg) after thrombectomy.<sup>73</sup> The trial showed a greater likelihood of poor functional outcome with the intensive target (odds ratio 1.37 (95% CI 1.07 to 1.76)). The OPTIMAL-BP trial in South Korea randomized 306 patients with large vessel occlusion stroke to intensive or conventional blood pressure management (systolic blood pressure targets of <140 mmHg and 140-180 mmHg respectively). This trial demonstrated potential harm with a more intensive blood pressure lowering strategy for patients with reperfusion by endovascular thrombectomy (adjusted odds ratio for functional independence 0.56 (0.33 to 0.96)).<sup>74</sup> Lastly, the recently published BEST-II trial randomized 120

patients after endovascular therapy to systolic blood pressure targets of <140, <160, or <180 mmHg and assessed infarct volume and functional outcomes.<sup>84</sup> These groups had no significant difference in infarct volumes, and the results suggest a low probability of benefit from lower blood pressure targets if tested in a larger trial.

#### *Cardiac emergencies*

Cardiac hypertensive emergencies include acute myocardial infarction and cardiogenic pulmonary edema with blood pressure >180/110 mmHg. In these presentations, afterload increases myocardial demand and strain, leading to ischemic symptoms or increased hydrostatic pressure causing pulmonary edema. Pulmonary edema is significantly more common than myocardial infarction, which is consistent with type 2 infarction, in which a mismatch in myocardial oxygen supply and demand causes ischemia and unstable coronary artery disease is absent.<sup>85</sup> Diagnosis requires a rise and fall in cardiac troponin above the 99th centile reference range. Indeterminant elevations in high sensitivity cardiac troponin below the 99th centile or any elevations that do not follow a pattern of rise and fall are not indicative of a type 2 myocardial infarction and do not indicate a hypertensive emergency. It is common for patients with acute severe hypertension to have chronic elevations in cardiac troponin, and these patients do not require immediate blood pressure lowering.

Blood pressure treatment is indicated when acute pulmonary edema or the less common type 2 myocardial infarction is present. The intensity of treatment is mild to moderate, largely based on expert opinion, and targets a 15-25% reduction in mean arterial pressure and relief of symptoms.<sup>77</sup> Nitroglycerin is a preferred agent and can be titrated to relief of chest pain and mean arterial pressure. Beta-blockade can reduce tachycardia and myocardial oxygen demand. Unless contraindicated, esmolol and intravenous labetalol are good second line agents. Nicardipine or clevidipine may also be beneficial if  $\beta$ blockers are contraindicated. For patients with acute cardiogenic pulmonary edema, nitroglycerin is also a preferred agent as it provides venodilation and preload reduction and afterload reduction at higher doses. Limited data indicate that high doses of nitroglycerin can be effective.<sup>75</sup> Nicardipine and clevidipine are also excellent agents to reduce afterload. These used in conjunction with a loop diuretic (such as furosemide or bumetanide) can provide rapid relief of symptoms due to pulmonary edema.

#### *Uncommon causes of hypertensive emergencies*

Less common causes of hypertensive emergencies include pheochromocytomas and drug induced hypertension. Little data exist to guide the intensity of blood pressure reduction, but moderate reduction of mean arterial pressure by 20-25% is a reasonable

approach to improve symptoms and reduce the potential for organ injury.

Pheochromocytomas release excess catecholamines leading to uncontrolled hypertension and can precipitate hypertensive emergency. Paroxysmal elevations in blood pressure are common in patients with pheochromocytoma, whereas the presence of the classic triad of episodic headache, diaphoresis, and tachycardia is less uniform.<sup>86</sup> The diagnosis of a pheochromocytoma is difficult and often confounded in the setting of hypertensive emergency as even contemporary biomarkers (such as plasma free metanephrines) can be significantly elevated.<sup>49–50</sup> A high index of suspicion is needed. In patients with newly identified or known pheochromocytoma, initial treatment with  $\alpha$  antagonists or calcium channel blockade is preferred.<sup>87</sup> Phentolamine is a preferred agent given its  $\alpha$  activity and rapid onset of action.<sup>88</sup> In the preoperative management before resection of a pheochromocytoma, phenoxybenzamine is the preferred  $\alpha$  blocker, but it is not indicated for acute management.<sup>89</sup> Nicardipine is a good choice added to phentolamine or as a standalone agent.<sup>90</sup> Initial treatment with  $\beta$  blocking antihypertensive agents, even labetalol, is contraindicated because of the low risk of paradoxical hypertension.

Sympathomimetic drugs can also lead to hypertensive emergencies. Epidemiological data are lacking on the degree to which such drugs contribute to various hypertensive emergency syndromes. In cases of suspected amphetamine, methamphetamine, or cocaine overdose, benzodiazepines should be considered as first line treatment to control clinical symptoms and secondarily to reduce blood pressure. Phentolamine is an acceptable agent given its  $\alpha$  antagonism for blood pressure control.<sup>88</sup> Nicardipine is a reasonable candidate for treatment.<sup>77</sup> Selective  $\beta$ -1 blockers are contraindicated. In clinical experience, labetalol, as a non-selective  $\beta$  blocker and  $\alpha$  adrenoceptor blocker, is safe and effective in these drug related hypertensive emergencies.<sup>77</sup>

### Emerging diagnostic and therapeutic options

#### Diagnostics

Incremental improvements in diagnostics related to hypertensive emergency, such as improved imaging for stroke, have occurred over the past decade. There remains a large gap, however, in suitable diagnostics for detecting underlying endothelial injury and autoregulatory failure related to hypertensive emergencies. Real time assessment of cerebral blood flow or cerebral perfusion pressure would allow for personalized approaches to blood pressure lowering within safe parameters based on autoregulation. Transcranial doppler ultrasound can provide surrogate assessments of cerebral blood flow and has been studied in suspected hypertensive emergency,<sup>91</sup> but it is challenging to implement in an emergency department, particularly for continuous measures. Near-infrared spectroscopy approaches to neuromonitoring have been in clinical use for many

years, such as in perioperative monitoring during major cardiac surgery.<sup>92</sup> While lacking precision and standardized methods for the bedside evaluation of hypertensive emergency, this technology continues to develop toward reliably assessing functional changes and may be an option for guiding treatment in hypertensive emergencies in the future.<sup>93</sup>

Ongoing research into the utility of biochemical markers for early recognition of pro-inflammatory states and endothelial damage is needed. The most promising biomarkers include endothelial and inflammatory markers.<sup>94</sup> Matrix metalloproteinases are enzymes that participate in the degradation of extracellular matrix when undergoing vascular remodeling and vasomotor changes.<sup>95–96</sup> Thrombomodulin, a transmembrane glycoprotein that is expressed on the surface of vascular endothelial cells, helps maintain vascular homeostasis and protects the endothelial bed. Circulating levels under normal physiologic conditions are low, and expression is elevated with vascular damage.<sup>97</sup> Endocan is secreted from endothelial cells to promote adhesion of leukocytes and is a potential marker of endothelial dysfunction in hypertension.<sup>98</sup> These different biomarkers could serve to improve identification of patients at risk of hypertensive emergency.<sup>93</sup>

#### Therapeutics

Blood pressure variability is an evolving therapeutic target in the management of neurological hypertensive emergencies. Post-hoc analysis of multiple randomized trials shows that increased blood pressure variability after the initial management of intracerebral hemorrhage is associated with worse neurologic outcomes.<sup>99–101</sup> This association was present with variability in the acute period (<24 hours from presentation) and the subacute time frame (up to 7 days). Further research on management strategies to target blood pressure variability may identify a different therapeutic target.

Preventive measures to mitigate hypertensive emergencies begin with public education and awareness of hypertension, initiation of therapy, and strategies to improve adherence. Data show that increased use of home blood pressure monitoring is a cost effective way to reduce adverse events.<sup>102</sup> Further research aimed at preventing hypertensive emergency through use of novel, patient-centered strategies and virtual care is ongoing. The potential role of team-based care (including pharmacists and community health workers) as well as remote monitoring of patients' vital signs in preventing recurrent hypertensive emergency should be investigated.

New therapeutic modalities may have a role in improving overall blood pressure control in patients at risk of hypertensive emergency, but they are unlikely to have a role in emergency care. These drugs include long acting aldosterone synthase inhibitors and RNA interference agents. A phase 2 trial on baxdrostat, a selective aldosterone synthase inhibitor, has

demonstrated efficacy.<sup>103</sup> Another phase 2 trial of a lorundrostat, an aldosterone synthase inhibitor, demonstrated systolic blood pressure reductions of up to 14 mm Hg over eight weeks.<sup>104</sup> Research on long acting injectable medications (such as zilebesiran) is ongoing, and antihypertensive medications that last six months have the potential to prevent episodes of hypertensive emergency.<sup>105</sup> The recently published phase 2 trial of zilebesiran, which targets hepatic angiotensinogen synthesis with RNA interference, showed efficacy in lowering blood pressure at six months after a single injectable dose.<sup>106</sup> Lastly, recent data on renal denervation demonstrate a modest reduction in blood pressure, and this therapeutic modality may have a role in treating patients with difficulty to control hypertension and mitigating hypertensive emergencies.<sup>107 108</sup>

### Guidelines

Several international societies, including the American Heart Association (AHA)/American College of Cardiology (ACC),<sup>17</sup> the European Society of Cardiology/European Society of Hypertension,<sup>18</sup> the British and Irish Hypertension Society,<sup>77</sup> and the International Society of Hypertension<sup>37</sup> have published guidelines about the management of severe hypertension and hypertensive emergencies. The strength of guidelines published by the British and Irish Hypertension Society is its focus on hypertensive emergency, whereas the other guidelines are broadly on hypertension management. In addition, the AHA, ASA, and ACC have published guidelines specific to stroke and vascular emergencies.<sup>78 81 83</sup> While minor differences in drug selection and treatment targets

exist, the above guidelines are unanimous in their emphasis on titratable blood pressure reduction for hypertensive emergencies, which includes an immediate reduction <25% followed by more gradual reduction. These guidelines agree that patients with severe elevations in blood pressure without signs of acute organ injury do not need emergency department evaluation or immediate blood pressure reduction with intravenous medications.

### Conclusions

Hypertensive emergency is a major global public health problem. When hypertensive emergencies are present, immediate attention toward careful blood pressure reduction with intravenous antihypertensive medications is indicated to reduce morbidity. When an emergency is absent and patients have acute severe hypertension, attention shifts to optimizing outpatient management with oral agents. Given the lack of randomized trials to guide management of hypertensive emergency, there remains a large unmet need for further research in these areas.

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### QUESTIONS FOR FUTURE RESEARCH

- Are there methods to personalize blood pressure lowering based on measurement of cerebral perfusion?
- Do medications that reduce blood pressure variability lead to improved outcomes in patients with hypertensive emergencies?
- What strategies will improve long term blood pressure control in emergency department patients with acute severe hypertension?

### HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients with hypertensive emergency or suspected hypertensive emergency participated in informal interviews with the writing team to inform the clinical perspective within the manuscript. Patients conveyed a common sense of anxiety and fear of stroke when they had severe blood pressure elevations. They also discussed frustrations related to transitions of care between the emergency department, hospital, and outpatient settings. These discussions particularly informed the writing and editing of the section on severely elevated blood pressure without emergency.

- 1 Wu P, Green M, Myers JE. Hypertensive disorders of pregnancy. *BMJ* 2023;381:e071653. doi:10.1136/bmj-2022-071653
- 2 World Health Organization. Hypertension. 2023. <https://www.who.int/news-room/fact-sheets/detail/hypertension>.
- 3 Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. *JAMA Intern Med* 2016;176:981-8. doi:10.1001/jamainternmed.2016.1509
- 4 Deshmukh A, Kumar G, Kumar N, et al. Effect of Joint National Committee VII report on hospitalizations for hypertensive emergencies in the United States. *Am J Cardiol* 2011;108:1277-82. doi:10.1016/j.amjcard.2011.06.046
- 5 Janke AT, McNaughton CD, Brody AM, Welch RD, Levy PD. Trends in the incidence of hypertensive emergencies in US emergency departments from 2006 to 2013. *J Am Heart Assoc* 2016;5:e004511. doi:10.1161/JAHA.116.004511
- 6 Francis-Morel G, Guevara NA, Malik M, Sotello D. Gender disparities in hypertensive emergency admissions: a national retrospective cohort study. *Cureus* 2023;15:e40287. doi:10.7759/cureus.40287
- 7 Waldron FA, Benenson I, Jones-Dillon SA, et al. Prevalence and risk factors for hypertensive crisis in a predominantly African American inner-city community. *Blood Press* 2019;28:114-23. doi:10.1080/08037051.2019.1568183
- 8 Benenson I, Waldron FA, Jadotte YT, Holly C. Risk factors for hypertensive crisis in adult patients: a systematic review protocol. *JBI Database System Rev Implement Rep* 2019;17:2343-9. doi:10.11124/JBISIRIR-2017-003996
- 9 Overgaauw N, Alsm J, Brink A, et al. Drug nonadherence is a common but often overlooked cause of hypertensive urgency and emergency at the emergency department. *J Hypertens* 2019;37:1048-57. doi:10.1097/HJH.0000000000002005
- 10 Benenson I, Waldron FA, Holly C. A Systematic Review and Meta-analysis of the Clinical and Epidemiological Characteristics of Patients with Hypertensive Emergencies: Implication for Risk Stratification. *High Blood Press Cardiovasc Prev* 2023;30:319-31. doi:10.1007/s40292-023-00586-1
- 11 Siddiqi TJ, Usman MS, Rashid AM, et al. Clinical Outcomes in Hypertensive Emergency: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2023;12:e029355. doi:10.1161/JAHA.122.029355

- 12 Muiasani ML, Salvetti M, Amadoro V, et al, Working Group on Hypertension, Prevention, Rehabilitation of the Italian Society of Cardiology, the Societa' Italiana dell'Ipertensione Arteriosa. An update on hypertensive emergencies and urgencies. *J Cardiovasc Med (Hagerstown)* 2015;16:372-82. doi:10.2459/JCM.0000000000000223
- 13 Chobanian AV, Bakris GL, Black HR, et al, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute/National High Blood Pressure Education Program Coordinating Committee. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-52. doi:10.1161/01.HYP.0000107251.49515.c2
- 14 Johnson W, Nguyen M-L, Patel R. Hypertension crisis in the emergency department. *Cardiol Clin* 2012;30:533-43. doi:10.1016/j.ccl.2012.07.011
- 15 National High Blood Pressure Education Program. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. National Heart, Lung, and Blood Institute, 2004.
- 16 Adebayo O, Rogers RL. Hypertensive emergencies in the emergency department. *Emerg Med Clin North Am* 2015;33:539-51. doi:10.1016/j.emc.2015.04.005
- 17 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018;138:e426-83.
- 18 Williams B, Mancia G, Spiering W, et al, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104. doi:10.1093/eurheartj/ehy339
- 19 Heath I. Hypertensive urgency-Is this a useful diagnosis? *JAMA Intern Med* 2016;176:988-9. doi:10.1001/jamainternmed.2016.1498
- 20 Mancia G, Kreuzer R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;41:1874-2071. doi:10.1097/HJH.0000000000003480
- 21 Dodson PM, Lip GY, Eames SM, Gibson JM, Beevers DG. Hypertensive retinopathy: a review of existing classification systems and a suggestion for a simplified grading system. *J Hum Hypertens* 1996;10:93-8.
- 22 Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1974;268:336-45. doi:10.1097/00000441-197412000-00004
- 23 Cremer A, Amraoui F, Lip GY, et al. From malignant hypertension to hypertension-MOD: a modern definition for an old but still dangerous emergency. *J Hum Hypertens* 2016;30:463-6. doi:10.1038/jhh.2015.112
- 24 Rubin S, Cremer A, Boulestreau R, Rigotherier C, Kuntz S, Gosse P. Malignant hypertension: diagnosis, treatment and prognosis with experience from the Bordeaux cohort. *J Hypertens* 2019;37:316-24. doi:10.1097/HJH.0000000000001913
- 25 Domek M, Gumprecht J, Lip GYH, Shantsila A. Malignant hypertension: does this still exist?. *J Hum Hypertens* 2020;34:1-4. doi:10.1038/s41371-019-0267-y
- 26 Boulestreau R, van den Born BH, Lip GYH, Gupta A. Malignant hypertension: current perspectives and challenges. *J Am Heart Assoc* 2022;11:e023397. doi:10.1161/JAHA.121.023397
- 27 Fuchs FD, Gus M, Gonçalves SC, Fuchs SC. Is it time to retire the diagnosis "hypertensive emergency"? *J Am Heart Assoc* 2023;12:e028494. doi:10.1161/JAHA.122.028494
- 28 Brandes RP. Endothelial dysfunction and hypertension. *Hypertension* 2014;64:924-8. doi:10.1161/HYPERTENSIONAHA.114.03575
- 29 Paulson OB, Waldemar G, Schmidt JF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. *Am J Cardiol* 1989;63:2C-5C. doi:10.1016/0002-9149(89)90396-2
- 30 Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973;1:507-10. doi:10.1136/bmj.1.5852.507
- 31 Strandgaard S. Cerebral blood flow in hypertension. *Acta Med Scand Suppl* 1983;678:11-25.
- 32 Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. *Hypertension* 2013;62:810-7. doi:10.1161/HYPERTENSIONAHA.113.01063
- 33 Ono M, Arnaoutakis GJ, Fine DM, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013;41:464-71. doi:10.1097/CCM.0b013e31826ab3a1
- 34 Strandgaard S. Cerebral ischaemia caused by overzealous blood pressure lowering. *Dan Med Bull* 1987;34(Suppl 1):5-7.
- 35 Al Adas Z, Shepard AD, Weaver MR, et al. Cerebrovascular injuries found in acute type B aortic dissections are associated with blood pressure derangements and poor outcome. *J Vasc Surg* 2018;68:1308-13. doi:10.1016/j.jvs.2018.01.056
- 36 Miller JB, Arter A, Wilson SS, et al. Appropriateness of bolus antihypertensive therapy for elevated blood pressure in the emergency department. *West J Emerg Med* 2017;18:957-62. doi:10.5811/westjem.2017.5.33410
- 37 Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* 2020;75:1334-57. doi:10.1161/HYPERTENSIONAHA.120.15026
- 38 Peixoto AJ. Acute severe hypertension. *N Engl J Med* 2019;381:1843-52. doi:10.1056/NEJMcp1901117
- 39 Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis. *Cardiol Rev* 2010;18:102-7. doi:10.1097/CRD.0b013e3181c307b7
- 40 Axon RN, Turner M, Buckley R. An update on inpatient hypertension management. *Curr Cardiol Rep* 2015;17:94. doi:10.1007/s11886-015-0648-y
- 41 Brathwaite L, Reif M. Hypertensive emergencies: a review of common presentations and treatment options. *Cardiol Clin* 2019;37:275-86. doi:10.1016/j.ccl.2019.04.003
- 42 Muiasani ML, Salvetti M, Amadoro V, et al, Working Group on Hypertension, Prevention, Rehabilitation of the Italian Society of Cardiology, the Societa' Italiana dell'Ipertensione Arteriosa. An update on hypertensive emergencies and urgencies. *J Cardiovasc Med (Hagerstown)* 2015;16:372-82. doi:10.2459/JCM.0000000000000223
- 43 Downie LE, Hodgson LA, Dsylvia C, et al. Hypertensive retinopathy: comparing the Keith-Wagener-Barker to a simplified classification. *J Hypertens* 2013;31:960-5. doi:10.1097/HJH.0b013e31823835efea3
- 44 Katz JN, Gore JM, Amin A, et al, STAT Investigators. Practice patterns, outcomes, and end-organ dysfunction for patients with acute severe hypertension: the Studying the Treatment of Acute hyperTension (STAT) registry. *Am Heart J* 2009;158:599-606.e1. doi:10.1016/j.ahj.2009.07.020
- 45 van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother* 2019;5:37-46. doi:10.1093/ehjcvp/pvy032
- 46 Vallelonga F, Carbone F, Benedetto F, et al. Accuracy of a symptom-based approach to identify hypertensive emergencies in the emergency department. *J Clin Med* 2020;9:2201. doi:10.3390/jcm9072201
- 47 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127-248. doi:10.1016/j.jacc.2017.11.006
- 48 Erdmann H. [Roentgenologic viewpoints on the definition of vertebral malposition]. *Hippokrates* 1967;38:427-32.
- 49 Amar L, Eisenhofer G. Diagnosing pheochromocytoma/paraganglioma in a patient presenting with critical illness: biochemistry versus imaging. *Clin Endocrinol (Oxf)* 2015;83:298-302. doi:10.1111/cen.12745
- 50 Murai S, Kakeshita K, Imamura T, et al. Malignant hypertension and bilateral primary aldosteronism. *Intern Med* 2023;62:2675-80. doi:10.2169/internalmedicine.1098-22
- 51 Börgel J, Springer S, Ghafoor J, et al. Unrecognized secondary causes of hypertension in patients with hypertensive urgency/emergency: prevalence and co-prevalence. *Clin Res Cardiol* 2010;99:499-506. doi:10.1007/s00392-010-0148-4
- 52 Talle MA, Doubell AF, Robbertse PS, Lahri S, Herbst PG. The role of cardiac biomarkers in the diagnosis of hypertensive emergency. *Diagnostics (Basel)* 2023;13:1605. doi:10.3390/diagnostics13091605
- 53 El Maraghi S, Yahia H, Heikal A, Ashraf M. B-type natriuretic peptide in hypertensive crises: Diagnostic use in hypertensive urgencies and emergencies. *Egypt J Crit Care Med* 2013;1:61-7. doi:10.1016/j.ejccm.2013.01.002
- 54 Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers and the risk of incident hypertension. *Hypertension* 2007;49:432-8. doi:10.1161/01.HYP.0000256956.61872.aa
- 55 Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol* 2017;264:1608-16. doi:10.1007/s00415-016-8377-8
- 56 Thomas W, Henry J, Chew JE, Premaratne M, Blecher G, Haji DL. Review article: Accuracy of emergency physician performed point-of-care ultrasound of the thoracic aorta: A systematic



- review and narrative synthesis of the literature. *Emerg Med Australas* 2023;35:720-30. doi:10.1111/1742-6723.14262
- 57 Maw AM, Hassanin A, Ho PM, et al. Diagnostic accuracy of point-of-care lung ultrasonography and chest radiography in adults with symptoms suggestive of acute decompensated heart failure: a systematic review and meta-analysis. *JAMA Netw Open* 2019;2:e190703. doi:10.1001/jamanetworkopen.2019.0703
- 58 Valleslonga F, Cesareo M, Menon L, et al. Hypertensive emergencies and urgencies: a preliminary report of the ongoing Italian multicentric study ERIDANO. *Hypertens Res* 2023;46:1570-81. doi:10.1038/s41440-023-01232-y
- 59 Van Bortel LM, Laurent S, Boutouyrie P, et al. Artery Society/European Society of Hypertension Working Group on Vascular Structure and Function/European Network for Noninvasive Investigation of Large Arteries. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012;30:445-8. doi:10.1097/HJH.0b013e32834fa8b0
- 60 Park SK, Lee DY, Kim WJ, et al. Comparing the clinical efficacy of resting and antihypertensive medication in patients of hypertensive urgency: a randomized, control trial. *J Hypertens* 2017;35:1474-80. doi:10.1097/HJH.0000000000001340
- 61 Mitsunegern T, Srimookda N, Imoun S, Wansupong S, Kotruchin P. The effect of pursed-lip breathing combined with number counting on blood pressure and heart rate in hypertensive urgency patients: A randomized controlled trial. *J Clin Hypertens (Greenwich)* 2021;23:672-9. doi:10.1111/jch.14168
- 62 Grossman E, Nadler M, Sharabi Y, Thaler M, Shachar A, Shamiss A. Antianxiety treatment in patients with excessive hypertension. *Am J Hypertens* 2005;18:1174-7. doi:10.1016/j.amjhyper.2005.03.728
- 63 Paštrović F, Okštajner PK, Vodanović M, et al. The role of anxiolytics in hypertensive urgency management. *Psychiatr Danub* 2020;32(Suppl 4):593-6.
- 64 Anderson TS, Herzog SJ, Jing B, et al. Clinical outcomes of intensive inpatient blood pressure management in hospitalized older adults. *JAMA Intern Med* 2023;183:715-23. doi:10.1001/jamainternmed.2023.1667
- 65 Rastogi R, Sheehan MM, Hu B, Shaker V, Kojima L, Rothberg MB. Treatment and outcomes of inpatient hypertension among adults with noncardiac admissions. *JAMA Intern Med* 2021;181:345-52. doi:10.1001/jamainternmed.2020.7501
- 66 Weder AB, Erickson S. Treatment of hypertension in the inpatient setting: use of intravenous labetalol and hydralazine. *J Clin Hypertens (Greenwich)* 2010;12:29-33. doi:10.1111/j.1751-7176.2009.00196.x
- 67 Levy PD, Mahn JJ, Miller J, et al. Blood pressure treatment and outcomes in hypertensive patients without acute target organ damage: a retrospective cohort. *Am J Emerg Med* 2015;33:1219-24. doi:10.1016/j.ajem.2015.05.036
- 68 Anderson CS, Heeley E, Huang Y, et al, INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368:2355-65. doi:10.1056/NEJMoa1214609
- 69 Song L, Hu X, Ma L, et al, INTERACT3 investigators. INTensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (INTERACT3): study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials* 2021;22:943. doi:10.1186/s13063-021-05881-7
- 70 Tang C, Zhang TS, Zhou LF. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: a meta-analysis. *PLoS One* 2014;9:e99536. doi:10.1371/journal.pone.0099536
- 71 Allison TA, Bowman S, Gulbis B, Hartman H, Schepcoff S, Lee K. Comparison of clevidipine and nicardipine for acute blood pressure reduction in patients with stroke. *J Intensive Care Med* 2019;34:990-5. doi:10.1177/0885066617724340
- 72 He J, Zhang Y, Xu T, et al, CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA* 2014;311:479-89. doi:10.1001/jama.2013.282543
- 73 Yang P, Song L, Zhang Y, et al, ENCHANTED2/MT Investigators. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial. *Lancet* 2022;400:1585-96. doi:10.1016/S0140-6736(22)01882-7
- 74 Nam HS, Kim YD, Heo J, et al, OPTIMAL-BP Trial Investigators. Intensive vs conventional blood pressure lowering after endovascular thrombectomy in acute ischemic stroke: The OPTIMAL-BP Randomized Clinical Trial. *JAMA* 2023;330:832-42. doi:10.1001/jama.2023.14590
- 75 Levy P, Compton S, Welch R, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. *Ann Emerg Med* 2007;50:144-52. doi:10.1016/j.annemergmed.2007.02.022
- 76 Campbell P, Baker WL, Bendel SD, White WB. Intravenous hydralazine for blood pressure management in the hospitalized patient: its use is often unjustified. *J Am Soc Hypertens* 2011;5:473-7. doi:10.1016/j.jash.2011.07.002
- 77 Kulkarni S, Glover M, Kapil V, et al. Management of hypertensive crisis: British and Irish Hypertension Society Position document. *J Hum Hypertens* 2023;37:863-79. doi:10.1038/s41371-022-00776-9
- 78 Isselbacher EM, Preventza O, Hamilton Black J3rd, Peer Review Committee Members. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;146:e334-482. doi:10.1161/CIR.0000000000001106
- 79 Gupta PK, Gupta H, Khoynezhad A. Hypertensive emergency in aortic dissection and thoracic aortic aneurysm—a review of management. *Pharmaceuticals (Basel)* 2009;2:66-76. doi:10.3390/ph2030066
- 80 Qureshi AI, Palesch YY, Barsan WG, et al, ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016;375:1033-43. doi:10.1056/NEJMoa1603460
- 81 Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2023;54:e314-70. doi:10.1161/STR.0000000000000436
- 82 Liu L, Xie X, Pan Y, et al, CATIS-2 Investigators. Early versus delayed antihypertensive treatment in patients with acute ischaemic stroke: multicentre, open label, randomised, controlled trial. *BMJ* 2023;383:e076448. doi:10.1136/bmj-2023-076448
- 83 Powers WJ, Rabinstein AA, Ackerson T, et al, American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-110. doi:10.1161/STR.0000000000000158
- 84 Mistry EA, Hart KW, Davis LT, et al. Blood pressure management after endovascular therapy for acute ischemic stroke: The BEST-II randomized clinical trial. *JAMA* 2023;330:821-31. doi:10.1001/jama.2023.14330
- 85 Thygesen K, Alpert JS, Jaffe AS, et al, Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018;138:e618-51. doi:10.1161/CIR.0000000000000617
- 86 Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. *Medicine (Baltimore)* 1991;70:46-66. doi:10.1097/00005792-199101000-00004
- 87 Bartkoski SR, Reschke DJ. Pheochromocytoma crisis in the emergency department. *Cureus* 2021;13:e13683.
- 88 Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*. 12th ed. McGraw Hill; 2011: 309.
- 89 Garg MK, Kharb S, Brar KS, Gundgurthi A, Mittal R. Medical management of pheochromocytoma: Role of the endocrinologist. *Indian J Endocrinol Metab* 2011;15(Suppl 4):S329-36. doi:10.4103/2230-8210.86976
- 90 Lebuffe G, Dosseh ED, Tek G, et al. The effect of calcium channel blockers on outcome following the surgical treatment of pheochromocytomas and paragangliomas. *Anaesthesia* 2005;60:439-44. doi:10.1111/j.1365-2044.2005.04156.x
- 91 Miller JB, Calo S, Reed B, et al. Cerebrovascular risks with rapid blood pressure lowering in the absence of hypertensive emergency. *Am J Emerg Med* 2019;37:1073-7. doi:10.1016/j.ajem.2018.08.052
- 92 Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke* 2010;41:1951-6. doi:10.1161/STROKEAHA.109.575159
- 93 Chen WL, Wagner J, Heugel N, et al. Functional near-infrared spectroscopy and its clinical application in the field of neuroscience: advances and future directions. *Front Neurosci* 2020;14:724. doi:10.3389/fnins.2020.00724
- 94 Andrade DO, Aguiar FL, Mansor ALP, et al. Inflammatory cytokines are associated to lower glomerular filtration rate in patients with hypertensive crisis. *Front Cardiovasc Med* 2022;9:969339. doi:10.3389/fcvm.2022.969339
- 95 Valente FM, de Andrade DO, Cosenso-Martin LN, et al. Plasma levels of matrix metalloproteinase-9 are elevated in individuals with hypertensive crisis. *BMC Cardiovasc Disord* 2020;20:132. doi:10.1186/s12872-020-01412-5
- 96 Yasmin A, McEniery CM, Wallace S, et al. Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:372. doi:10.1161/01.ATV.0000151373.33830.41

- 97 Guo XQ, Ren W, Peng R, Liu YH, Li Y. Clinical application of endothelial injury marker in hypertensive patients. *J Clin Lab Anal* 2018;32:e22387. doi:10.1002/jcla.22387
- 98 Behnouth AH, Khalaji A, Bahiraie P, et al. Endocan as a marker of endothelial dysfunction in hypertension: a systematic review and meta-analysis. *Hypertens Res* 2023;46:2388-99. doi:10.1038/s41440-023-01402-y
- 99 de Havenon A, Majersik JJ, Stoddard G, et al. Increased blood pressure variability contributes to worse outcome after intracerebral hemorrhage. *Stroke* 2018;49:1981-4. doi:10.1161/STROKEAHA.118.022133
- 100 Manning L, Hirakawa Y, Arima H, et al, INTERACT2 investigators. 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. doi:10.1016/S1474-4422(14)70018-3
- 101 Chung PW, Kim JT, Sanossian N, et al, FAST-MAG Investigators and Coordinators. Association between hyperacute stage blood pressure variability and outcome in patients with spontaneous intracerebral hemorrhage. *Stroke* 2018;49:348-54. doi:10.1161/STROKEAHA.117.017701
- 102 Li Y, Zhang D, Li W, et al. The health and economic impact of expanding home blood pressure monitoring. *Am J Prev Med* 2023;65:775-82. doi:10.1016/j.amepre.2023.05.010
- 103 Freeman MW, Halvorsen YD, Marshall W, et al, BrightHTN Investigators. Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N Engl J Med* 2023;388:395-405. doi:10.1056/NEJMoa2213169
- 104 Laffin LJ, Rodman D, Luther JM, et al, Target-HTN Investigators. Aldosterone synthase inhibition with lorundrostat for uncontrolled hypertension: The Target-HTN randomized clinical trial. *JAMA* 2023;330:1140-50. doi:10.1001/jama.2023.16029
- 105 Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med* 2023;389:228-38. doi:10.1056/NEJMoa2208391
- 106 Bakris GL, Saxena M, Gupta A, et al, KARDIA-1 Study Group. RNA interference with zilebesiran for mild to moderate hypertension: The KARDIA-1 randomized clinical trial. *JAMA* 2024;331:740-9. doi:10.1001/jama.2024.0728
- 107 Azizi M, Saxena M, Wang Y, et al, RADIANCE II Investigators and Collaborators. Endovascular ultrasound renal denervation to treat hypertension: The RADIANCE II randomized clinical trial. *JAMA* 2023;329:651-61. doi:10.1001/jama.2023.0713
- 108 Kirtane AJ, Sharp ASP, Mahfoud F, et al, RADIANCE Investigators and Collaborators. Patient-level pooled analysis of ultrasound renal denervation in the sham-controlled RADIANCE II, RADIANCE-HTN SOLO, and RADIANCE-HTN TRIO trials. *JAMA Cardiol* 2023;8:464-73. doi:10.1001/jamacardio.2023.0338