

## AHA SCIENTIFIC STATEMENT

# Orthostatic Hypotension in Adults With Hypertension: A Scientific Statement From the American Heart Association

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**ABSTRACT:** Although orthostatic hypotension (OH) has long been recognized as a manifestation of autonomic dysfunction, a growing body of literature has identified OH as a common comorbidity of hypertension. This connection is complex, related to pathophysiology in blood pressure regulation and the manner by which OH is derived as the difference between 2 blood pressure measurements. While traditional therapeutic approaches to OH among patients with neurodegenerative disorders focus on increasing upright blood pressure to prevent cerebral hypoperfusion, the management of OH among patients with hypertension is more nuanced; resting hypertension is itself associated with adverse outcomes among these patients. Although there is substantial evidence that intensive blood pressure treatment does not cause OH in the majority of patients with essential hypertension, some classes of antihypertensive agents may unmask OH in patients with an underlying autonomic impairment. Practical steps to manage OH among adults with hypertension start with (1) a thorough characterization of its patterns, triggers, and cause; (2) review and removal of aggravating factors (often pharmacological agents not related to hypertension treatment); (3) optimization of an antihypertensive regimen; and (4) adoption of a tailored treatment strategy that avoids exacerbating hypertension. These strategies include countermaneuvers and short-acting vasoactive agents (midodrine, droxidopa). Ultimately, further research is needed on the epidemiology of OH, the impact of hypertension treatment on OH, approaches to the screening and diagnosis of OH, and OH treatment among adults with hypertension to improve the care of these patients and their complex blood pressure pathophysiology.

**Key Words:** AHA Scientific Statements ■ antihypertensive agents ■ blood pressure ■ comorbidity ■ hypertension ■ hypotension, orthostatic

Hypertension affects nearly half of US adults<sup>1</sup> and >1 billion adults worldwide.<sup>2</sup> Although there is indisputable benefit to more intensive control of hypertension in the general population to prevent cardiovascular disease,<sup>3</sup> hypertension treatment is often complicated by the presence of orthostatic hypotension (OH), defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (BP) of at least 10 mm Hg within 3 minutes of standing.<sup>4</sup> Common among adults with uncontrolled hypertension,<sup>5</sup> OH is frequently cited as a consequence of hypertension treatment.<sup>6</sup> Moreover, antihypertensive treatment guidelines recommend screening for OH (1) before the initiation or escalation of therapy and (2) in the setting of treatment to prevent hypotensive adverse events.<sup>7</sup> However, recent

evidence has prompted a reconsideration of OH as a limiting factor for hypertension management. The present scientific statement focuses on the latest science with respect to the epidemiology and complex pathophysiology between OH and hypertension, approaches to OH screening and monitoring, the impact of hypertension treatment on OH, treatment strategies among adults with OH and hypertension, and recommendations for further research.

## EPIDEMIOLOGY

The prevalence of OH is highly variable on the basis of study inclusion criterion and screening procedures. Nevertheless, OH prevalence increases with age and with

disease burden. OH is estimated to affect  $\approx 10\%$  of adults  $\geq 60$  years of age and increases to 16% to 30% among adults  $> 65$  years of age.<sup>8,9</sup> Moreover, it affects 50% to 65% of institutionalized older adults<sup>10</sup> and as many as 10% of adults with hypertension.<sup>11–13</sup> OH also disproportionately affects adults with diabetes, heart failure, and chronic kidney disease and is strongly associated with sarcopenia and frailty.<sup>10,14–17</sup> Population-based studies have examined the prevalence of OH by race or ethnicity and by sex in patients with hypertension with mixed findings. In the ARIC (Atherosclerosis Risk in Communities Study) cohort, OH was more common among Black adults than White adults (6.4% versus 4.4%),<sup>18</sup> whereas OH was more prevalent among women and among White participants compared with Black participants in ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP trial<sup>19</sup> and SPRINT (Systolic Blood Pressure Intervention Trial).<sup>20</sup>

OH is an independent risk factor of mortality and cardiovascular comorbidities linked to increased hospital admissions.<sup>8,21,22</sup> A meta-analysis of 15 cohort studies found that individuals with OH had a higher risk of developing heart failure, atrial fibrillation, coronary heart disease, and myocardial infarction.<sup>22</sup> In a number of population-based longitudinal and prospective studies, OH has been a consistent predictor of a higher risk of coronary events, ischemic stroke, cardiovascular disease, and asymptomatic atrial fibrillation.<sup>8</sup> These study findings suggest that OH may be a robust yet underrecognized risk factor of cardiovascular disease–related morbidity and mortality, especially among older adults.

OH is also associated with a number of noncardiovascular adverse outcomes, including falls,<sup>23–27</sup> fractures,<sup>27–29</sup> syncope,<sup>28,31,32</sup> cognitive decline or dementia,<sup>27,33–35</sup> depression,<sup>36</sup> frailty,<sup>23</sup> and early death.<sup>27,28</sup> Whether OH is a causal factor in the development of these adverse outcomes is a focus of ongoing debate. It is thought that hypoperfusion of skeletal muscle, heart, and brain may cause progressive organ injury, contributing to subclinical damage and progressive declines in function. However, emerging evidence also suggests a role for comorbid hypertension in the supine or seated positions as the primary driver of injury and adverse outcomes.<sup>37</sup> It is equally possible that the combination of high and low BP, that is, BP variability, may drive clinical events.

Last, many studies on OH identify adults with asymptomatic OH as a result of a standardized protocol. This is an important distinction from clinic cohorts in which OH is identified in response to a symptom or clinical event. Both orthostatic symptoms and asymptomatic measured OH have been associated with adverse events.<sup>34,38</sup> Moreover, orthostatic symptoms have been associated with missing data in cohort studies (ie, being too symptomatic to stand for BP measurement),<sup>34</sup> and there are many cases of OH not being perceived among patients.<sup>39</sup> Together, this nonstandard symptom capture and selection has led to conflicting conclusions across the OH literature.<sup>40</sup>

## PATHOPHYSIOLOGY

OH is driven by gravitational redistribution of  $\approx 300$  to 800 cm<sup>3</sup> of fluid to the lower extremities and splanchnic vessels upon standing.<sup>41,42</sup> In the healthy adult, this drop in pressure is sensed by baroreceptors in the carotid arteries and right atrium, resulting in an autonomic reflex that promotes a number of physiological responses, most prominently sympathetic vasoconstriction ( $\alpha$ -adrenergic response), increased heart rate (parasympathetic withdrawal and  $\beta$ -adrenergic response), and increased venous return through splanchnic venous bed compression and skeletal muscle contraction.<sup>42,43</sup> Impairments in both autonomic or individual response pathways can contribute to OH. Some forms of autonomic failure are sufficient to explain OH, but in most patients, OH results from a combination of impaired autonomic reflexes and volume depletion or adverse effects of medications.<sup>44</sup> OH should be distinguished from postural tachycardia syndrome, a chronic orthostatic intolerance condition associated with significantly increased heart rate upon standing without a drop in BP.<sup>45</sup>

## OH Characterization

To individualize OH treatment, a critical first step is to consider its underlying cause and to characterize relevant BP patterns (Table). With respect to causes, the occurrence of OH implies that autonomic mechanisms are unable to compensate for the challenges of upright posture. The degree of autonomic impairment is a continuum. On one extreme is neurogenic OH, seen in neurodegenerative disorders and peripheral autonomic neuropathies and caused by neurodegeneration of central autonomic pathways or denervation of peripheral sympathetic nerves. OH is the consequence of impaired sympathetic vasoconstriction due to reduced norepinephrine release from postganglionic neurons and is independently associated with increased mortality.<sup>46</sup> Clinically, these conditions are less common in the general population, and the pattern of OH tends to be more sustained, highly reproducible, and of larger magnitude and entails higher risk of adverse events related to cerebral hypoperfusion such as syncope or falls.

The term nonneurogenic OH is often used to describe cases of OH that occur in patients who have some degree of autonomic impairment caused by aging, diabetes, or other neuropathies and in combination with aggravating factors, often volume depletion or the use of medications that impair compensatory mechanisms that maintain orthostatic tolerance.<sup>40</sup> A more rigorous term arguably would be OH with a nonneurogenic component. There is growing enthusiasm for the ratio of orthostatic change in heart rate to change in SBP as a screening tool to indicate the presence of underlying autonomic impairment, causing an inappropriate heart rate response (a

**Table. Conditions, Mechanisms, and Impact of Hypertension Treatment on Various Clinical Presentations of OH**

Diagnosis	Mechanism	Predominant pattern	Effect of hypertension treatment	Related conditions
Classic OH	Autonomic dysfunction	Low standing BP with or without supine hypertension Often symptomatic	Worse upright hypotension; improved supine hypertension	Parkinson disease, pure autonomic failure
Hypertensive OH	Reduced diastolic filling due to left ventricular hypertrophy; arterial stiffness	High supine/seated BP, normal standing BP Often asymptomatic	Reduced incidence with improved BP regulation	Hypertension, left ventricular hypertrophy, atherosclerotic disease
Pseudo-OH, threshold effect* (see Supplemental Figure)	Similar percent change at higher BP exceeds the BP threshold used to define OH	High supine/seated BP Asymptomatic	Reduced incidence with lower resting BP	Hypertension
Pseudo-OH, measurement error† (see Figure 2)	Greater measurement error with higher resting BP can cause the appearance of a large change in BP if the first error goes opposite to the second error.	Transient/nonreproducible Asymptomatic	Lower BP variability with lower resting BP	Hypertension, BP lability

BP indicates blood pressure; and OH, orthostatic hypotension.

\*It has been recommended to use a systolic change threshold of 30 mmHg among patients with hypertension to address this concern.

†This issue also affects orthostatic hypertension.

ratio <0.5 is strongly associated with neurogenic OH).<sup>47</sup> Conversely, and of practical importance, a ratio >0.5 suggests the presence of aggravating and potentially reversible factors.

OH is also more likely to be observed among adults with hypertension, in part because of its derivation as the difference of 2 BP measurements. That is, the magnitude of changes in BP used to define OH is more likely to be observed among adults with elevated supine BPs (see Supplemental Figure). Nevertheless, OH is also associated with a number of hypertension patterns that may be informative for personalizing treatment strategies. The patterns with the most consistent evidence are (1) white-coat effect, (2) nocturnal hypertension or nondipping, and (3) morning hypotension. Multiple studies have demonstrated that OH is related to the white-coat phenomenon: elevated BP in clinic and lower BP outside of clinic.<sup>48</sup> One study involving 4305 patients with hypertension demonstrated that early OH (OH within 1 minute of standing) was present in ≈7% of those with white-coat hypertension.<sup>49</sup> Another study examining 897 adults (a subpopulation of SPRINT) undergoing BP treatment showed that OH was positively associated with white-coat effects.<sup>50</sup>

Another common pattern is nocturnal nondipping (ie, the absence of a normal drop in BP while asleep) or nocturnal hypertension (high BP while sleeping),<sup>50–53</sup> which may be more pronounced in older adults because of aging-related changes in circadian BP regulation<sup>54</sup> and could reflect an incipient neurodegenerative disorder (see the discussion of neurogenic OH).<sup>55</sup> Furthermore, reverse dipping (nighttime BP greater than daytime BP) is associated with the most pronounced OH in elderly adults with hypertension with diabetes.<sup>56</sup> This pattern is often coupled with yet a third common presentation of OH, morning hypotension,<sup>57</sup> which is thought to reflect a transient hypovolemic state secondary to pressure natriuresis driven by high BP while supine overnight (Figure 1).<sup>58</sup>

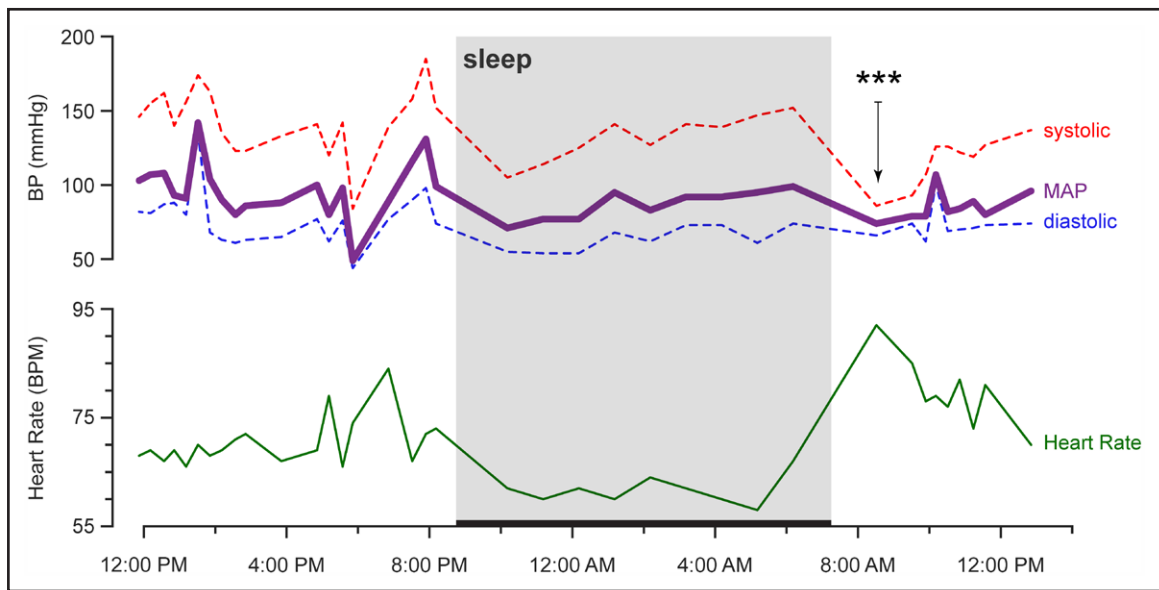
Last, it is important to consider OH in the context of BP measurement. BP varies substantially within each person, with the SD of SBPs ranging from 10 to >20 mmHg, depending on the device and approach used. The higher the BP is, the greater its variability. Any time 2 measurements are obtained, it is possible to observe a difference that meets the criteria for OH as a result of random error (Figure 2).<sup>59</sup> Thus, in studies that rely on single assessments of asymptomatic OH, a proportion of the OH prevalence will be secondary to measurement error and thus linked spuriously to hypertension.

## HYPERTENSION TREATMENT AND OH

### Treatment Goal and OH

The relationship among hypertension, drug therapy, and OH is both nuanced and complex. OH is more prevalent when BP is uncontrolled than when it is controlled.<sup>60,61</sup> Moreover, targeting a lower BP goal does not appear to cause OH in the majority of patients with essential hypertension and, in fact, may reduce its occurrence.<sup>9,19,62,63</sup> It should be noted, however, that patients with symptomatic OH are typically excluded from hypertension trials.<sup>40</sup> Although intensive pharmacological treatment to a goal SBP <120 mmHg in SPRINT did not alter the association of OH (mostly asymptomatic) with hypotension-related hospitalizations/emergency department visits or bradycardia,<sup>9</sup> intensive treatment did increase the risk for hypotensive episodes and syncope.<sup>64</sup> Therefore, it is important to consider the severity of the patient's autonomic impairment. Whereas the majority of patients with hypertension will tolerate and benefit from intensive hypertension treatment, the management of patients with severe forms of neurogenic OH may need to be individualized.

Questions remain as to whether clinicians should evaluate standing SBP level independently of orthostatic

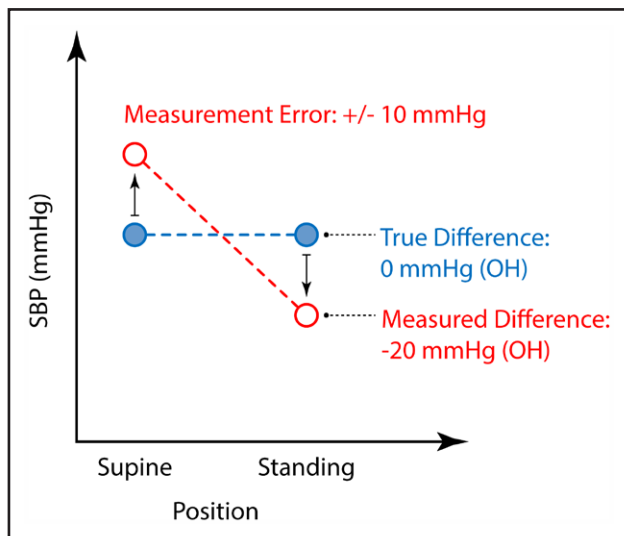


**Figure 1. Twenty-four-hour ambulatory BP monitor recording of a patient recently hospitalized for syncope and treated with fludrocortisone for suspected neurogenic OH.**

The reading is notable for blood pressure variability, nocturnal hypertension, and a morning drop in blood pressure after a short walk that correlated with severe lightheadedness (denoted by \*\*\*). Sleep period is depicted with a thick horizontal line between 8:45 PM and 7:45 AM. Orthostatic vitals the day after ambulatory monitoring were consistent with orthostatic hypotension (OH) on the basis of the following systolic blood pressures/diastolic blood pressures/heart rates: 175 mmHg/82 mmHg/67 bpm (supine), 152 mmHg/79 mmHg/70 bpm (seated), 109 mmHg/67 mmHg/72 bpm ( $\approx$ 1 minute standing), and 115 mmHg/67 mmHg/73 bpm ( $\approx$ 3 minutes of standing). BP indicates blood pressure; and MAP, mean arterial pressure.

fall in BP during the care of patients actively treated for hypertension. One study in older community-dwelling adults found that a lower standing SBP predicted falls, whereas conventional definitions of OH did not,<sup>65</sup> suggesting that low upright BP may be of greater concern among treated patients with hypertension than the

worsening of OH, as long as upright BP is maintained above the threshold of cerebral autoregulation that triggers hypoperfusion (Supplemental Figure). Control of BP throughout the 24-hour cycle also may prove elusive given the predilection for reverse or nondipping nocturnal hypertension in patients with OH.<sup>50,52</sup>



**Figure 2. The higher the resting SBP, the greater the variability and the potential for differences that meet the definition of OH, but are actually secondary to measurement error ( $\pm 10$  mmHg).**

OH indicates orthostatic hypotension; and SBP, systolic blood pressure.

### Antihypertensive Classes and OH

Although there is substantial evidence that intensive BP lowering in randomized controlled trials reduces the risk of OH,<sup>63</sup> few studies have addressed the effect of individual drug classes. It should also be noted that many large hypertension trials with OH measurements did not reflect the range of antihypertensive agents used in clinical practice.<sup>63</sup> Furthermore, patients with severe forms of OH and subgroups with dementia or diabetes were generally not included in trials.<sup>40</sup> Observational studies have shown associations between OH and number<sup>20</sup> or class of antihypertensive agents.<sup>66</sup> Nevertheless, this should not be conflated to imply causality because of the confounding influence of hypertension, especially uncontrolled hypertension, that accompanies hypertension treatments.

Given that the sympathetic nervous system plays a critical role in controlling compensatory responses to changes in posture, it is not surprising that drugs that impair these compensatory mechanisms are associated with OH (Figure 3). Indeed, in observational studies,

<b>Higher Risk</b>			
<b>Class</b>	<b>Examples</b>	<b>Mechanism</b>	
Alpha-1-blocker	Doxazosin, prazosin, terazosin	Adrenergic inhibition	
Central alpha agonist	Clonidine, guanfacine	Adrenergic inhibition	
Peripheral alpha agonists	Reserpine	Adrenergic inhibition	
Vasodilating beta blockers	Carvedilol, labetalol, nebivolol	Adrenergic inhibition	
Beta blockers	Atenolol, metoprolol, propranolol	Adrenergic inhibition	
Direct vasodilators	Hydralazine, minoxidil	Vasodilation	
Nitrates	Nitroglycerin, isosorbide dinitrate	Vasodilation	
Phosphodiesterase inhibitors	Sildenafil, tadalafil	Vasodilation	
Nondihydropyridine calcium channel blockers	Diltiazem, verapamil	Adrenergic inhibition	
Loop diuretics	Furosemide, torsemide	Hypovolemia	
Dihydropyridine calcium channel blockers (CCB)*	Amlodipine, nifedipine	Vasodilation	
Thiazide/thiazide-like/thiazide-type diuretics*	Chorthalidone, hydrochlorothiazide, indapamide	Hypovolemia	
Potassium sparing diuretics	Amiloride, triamterene	Hypovolemia	
Aldosterone blockers	Eplerenone, spironolactone	Hypovolemia	
Angiotensin-converting enzyme inhibitors (ACEi)*	Lisinopril	RAAS Inhibition	
Angiotensin receptor blockers (ARB)*	Losartan, valsartan	RAAS Inhibition	
<b>Lower Risk</b>			

**Figure 3. Relative ranking of hypertension classes according to risk of OH.**

There is a scarcity of evidence on this topic, representing an important research priority. OH indicates orthostatic hypotension; and RAAS, renin-angiotensin-aldosterone system.

\*A class considered first-line treatment for hypertension treatment.

peripheral  $\alpha$ -blockers,<sup>12,66,67</sup>  $\beta$ -blockers,<sup>12,66,68,69</sup> and central sympatholytics<sup>12</sup> are associated with OH. Among individual classes of antihypertensives,  $\beta$ -blocker monotherapy increased the odds of initial OH and sustained OH 2- and 3-fold, respectively.<sup>68,69</sup> In Black adults with chronic kidney disease, metoprolol was associated with OH compared with ramipril and amlodipine.<sup>62</sup>

Thiazide diuretics have been associated with OH in some<sup>12,66,67</sup> but not all<sup>70</sup> observational studies. Loop diuretics, possibly by inducing intravascular volume depletion, have also been linked to OH.<sup>66</sup>

Calcium channel blockers have been associated with greater fluctuations in OH, but these studies do not consistently differentiate between dihydropyridine and nondihydropyridine calcium channel blockers,<sup>20</sup> and some studies show no association.<sup>66,68</sup> In a secondary analysis of the ALLHAT study (Antihypertensive and Lipid-Lowering

Treatment to Prevent Heart Attack), amlodipine was not associated with a higher risk of diagnostic codes for OH compared with lisinopril or chlorthalidone, but it was associated with higher risk of falls in the short term.<sup>70</sup>

Results for renin-angiotensin system blockers (eg, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) are less consistent, showing a reduction in OH in patients attending a hypertension clinic,<sup>12</sup> no difference in OH in an Irish population study of adults  $\geq 50$  years of age,<sup>68</sup> and a higher risk of OH in community-dwelling women in the United Kingdom.<sup>66</sup> In older adults with dementia, OH was related to nitrates, combinations of angiotensin-converting enzyme inhibitors and diuretics, and combinations of angiotensin-converting enzyme inhibitors and nitrates.<sup>71</sup>

Of note, first-line drug classes in the 2017 American College of Cardiology/American Heart Association



guidelines<sup>7</sup> are all lower-risk drugs for causing OH (Figure 3). Moreover, the most effective drug combinations (renin-angiotensin system blockers and thiazides or calcium channel blockers) are lower risk for OH.

## DIAGNOSTIC PROTOCOLS FOR OH AND RECOMMENDATIONS FOR SCREENING

The most sensitive and consistent orthostatic BP measurements are obtained early in the morning, when symptoms tend to be most severe. However, there is substantial variability with how OH is assessed.<sup>16</sup> In general, it is recommended to measure BP after 5 to 10 minutes in the supine position and within 3 minutes after the standing position is assumed.<sup>4</sup> Although this protocol may not account for all known patterns of OH, it will capture many cases of clinically significant OH. More research is needed to define the ideal timing of upright BP measurements and their association with clinical outcomes. Initial OH is a transient decrease in BP within the first 15 seconds of standing<sup>72</sup> that can be associated with vasovagal syncope but is usually not evidence of neurogenic OH. Initial OH can be detected only by continuous beat-to-beat BP monitoring<sup>24,37,73</sup> or by the transient nature of OH symptoms in the clinical history. Delayed-recovery OH<sup>72</sup> is also a transient event that resolves within 2 to 3 minutes of standing and can be associated with falls. Timing of assessment directly affects the prevalence of OH detected, with earlier OH assessments identifying more OH.<sup>74</sup> Furthermore, there are data suggesting that BP change within 1 minute of upright posture is more closely related to dizziness and adverse health outcomes.<sup>28</sup> Last, delayed OH<sup>75</sup> occurs after 3 minutes of standing and is associated with progression to autonomic failure.<sup>76</sup> It should be suspected in patients with typical postural-related symptoms and a negative 3-minute postural test. This highlights the importance of both a thorough clinical history and repeated orthostatic BP measurements. Orthostatic symptom assessments are also important. In some studies, orthostatic dizziness has been a more sensitive predictor of neurological outcomes than OH measured at 3 minutes of standing,<sup>34</sup> whereas others highlight the fact that orthostatic symptoms can be absent in patients with documented OH<sup>39</sup> and in patients with dementia.<sup>77</sup>

Large hypertension treatment trials have used seated-to-standing rather than supine-to-standing BP protocols to detect OH.<sup>19,20,63,78</sup> Seated-to-standing protocols are included as an alternative method in many society guidelines,<sup>16</sup> and are more practical and easier to implement, particularly in ambulatory clinics and large clinical trials, but at the cost of decreased sensitivity<sup>79</sup> because OH is diagnosed more frequently from supine than from seated positions.<sup>24,37,73,80–83</sup> Moreover, 1 study found that only supine-to-standing OH was associated with falls and orthostatic symptoms in adults  $\geq 70$  years of age (62% hypertensive).<sup>83</sup>

A lower seated BP change threshold (15/7 mmHg) has been suggested as an alternative definition for seated-to-standing protocols for detecting conventionally defined supine OH,<sup>81</sup> although this finding, derived in a younger population of neurology patients, has not been replicated in frailer or older populations, in whom hypertension is more common.<sup>83,84</sup> Others have recommended a more specific definition for OH in the setting of hypertension, that is, a drop in SBP of 30 mmHg (versus 20 mmHg). However, such a change would mitigate threshold effects at the expense of reduced sensitivity (Table and Supplemental Figure).<sup>78</sup>

The diagnosis of OH can be made with an active standing test or with a tilt table test; active stand presents a greater challenge to cardiovascular reflexes than head-up tilt<sup>85,86</sup> and is easier to implement. Manual or preprogrammed oscillometric sphygmomanometers are the most commonly used technologies in recent antihypertensive drug trials.<sup>64,87</sup> OH detection is also influenced by time of day (highest in the morning),<sup>88</sup> meals,<sup>89,90</sup> alcohol (vasodilator properties and through impaired vasoconstriction/blunted sympathetic response to standing),<sup>91–93</sup> vigorous exercise,<sup>94</sup> timing of hypertension medications, and duration of rest.<sup>79,95</sup> Frail older patients may take longer to stand and thus have less marked immediate OH.<sup>96</sup> New orthostatic symptoms or OH-related adverse clinical outcomes may herald new-onset OH in previously unaffected patients.

A practical clinical issue is who should be routinely screened for OH. The American College of Cardiology/American Heart Association guidelines<sup>7</sup> and the European Society of Cardiology/European Society of Hypertension guidelines<sup>97</sup> recommend obtaining orthostatic BP measurements at the initial visit in all patients with hypertension. Moreover, the American College of Cardiology/American Heart Association guidelines recommend evaluation for OH in follow-up after initiation of antihypertensive therapy and in higher-risk groups such as older adults.<sup>7</sup> The American Autonomic Society recommends screening patients with neurodegenerative diseases such as Parkinson disease,<sup>89</sup> and the American Diabetes Association recommends regular OH screening as part of hypertension care among adults with diabetes.<sup>98</sup>

## PRACTICAL STEPS TO MANAGE OH IN ADULTS WITH HYPERTENSION

The coexistence of OH and hypertension represents a management dilemma, and the challenge is to treat one without having a significant impact on the other.

1. Characterize patterns, triggers, and cause. Characterization of BP pattern throughout the day and identification of OH triggers represent critical first steps for both prevention and individualized care. For example, identifying time periods or activities that trigger OH can inform plans to optimize

the management of both conditions. Moreover, characterization of pattern can aid in the diagnosis of the underlying cause of OH, which can inform treatment strategy. Removing exacerbating medications, addressing aggravating factors (eg, anemia or volume depletion), and implementing nonpharmacological strategies represent first-line approaches in all cases. For symptomatic neurogenic OH, pharmacological treatment that increases upright BP may be necessary. It is important to differentiate causes of OH to avoid exacerbating comorbid hypertension.

2. Optimize contributory medications
  - a. Nonantihypertensive medications. One of the first steps in treating OH is to remove medications with potential adverse effects. This starts with a comprehensive review of prescription and over-the-counter medications. Among nonantihypertensive medications, tricyclic antidepressants<sup>99</sup> (notably amitriptyline), trazodone (because of its  $\alpha$ -blocking properties),<sup>100</sup> and dopaminergic agents are common culprits,<sup>41</sup> in part because they are used in populations already at risk for OH (patients with peripheral neuropathies, older adults, and patients with Parkinson disease, respectively).<sup>101</sup> Tizanidine, commonly prescribed in the United States as a central muscle relaxant, is a central sympatholytic related to clonidine that can induce a clinical picture of neurogenic OH with abnormal cardiovascular reflexes, especially among those taking strong CYP1A2 inhibitors.<sup>102,103</sup> "Uroselective"  $\alpha$ -1a receptor antagonists (eg, tamsulosin) that preferentially relax the smooth muscle in the bladder and urethra are commonly prescribed for benign prostatic hyperplasia and are known to increase the incidence of severe OH, requiring hospital admissions.<sup>104</sup>

It is also important to consider the severity of the patient's autonomic impairment. For example, some medications known to alter BP such as sildenafil may be generally well-tolerated in patients with hypertension but can decrease BP by  $\approx$ 30 mmHg in patients with severe autonomic failure.<sup>105</sup>
  - b. Antihypertensive medications. Most patients with essential hypertension can be treated with recommended first-line antihypertensive agents without exacerbation of OH. Moreover, there is little evidence that a less intensive treatment goal will reduce OH.<sup>63</sup> In addition, given the close relationship between OH and hypertension, removing antihypertensives could worsen symptoms and risk for OH. Thus, removing first-line antihypertensive agents should not be an immediate response for patients with

hypertension found to have OH. Instead, regimens should be optimized, and antihypertensive medications known to be associated with OH such as  $\alpha$ -blockers,  $\beta$ -blockers, and centrally acting sympatholytic agents<sup>16</sup> should be discontinued, dose reduced, or substituted for more favorable classes (see the Antihypertensive Classes and OH section). Patients should be monitored carefully after changes in antihypertensive drug therapy are made because there may be increased risk of orthostatic symptoms and falls in the period soon after change in antihypertensive medications, particularly among older adults.<sup>106,107</sup>

3. Nonpharmacological approaches
  - a. Countermeasures. Compression garments applied to the lower body have been used to treat OH by improving venous return but are difficult for patients to apply at a constant effective pressure. An alternative option is an abdominal binder, which can be as effective in improving upright BP as the  $\alpha$ -agonist midodrine.<sup>108</sup> This has the advantage of selectively improving upright BP without worsening seated or supine hypertension. No clinical studies have demonstrated the tolerability and long-term efficacy of this approach, and patient compliance is often a limitation.
  - b. Fluid and sodium—caution. Expanding intravascular volume is thought to minimize the decline in BP while standing among patients with OH.<sup>109</sup> Moreover, some experts recommend that patients with OH would benefit from increasing their sodium intake to 10 g sodium chloride per day.<sup>110</sup> However, the beneficial effect of enhancing salt intake on OH has to be balanced with the risk of worsening supine hypertension and pressure natriuresis.<sup>72</sup>

In patients with severe OH, drinking  $\approx$ 500 mL of water has been shown to improve standing BP in small studies.<sup>111–113</sup> Most patients in these studies had severe underlying autonomic dysfunction. For example, in a study involving 11 patients, the mean standing SBP improved from 83 mmHg at baseline to 114 mmHg approximately half an hour after the patient drank water. It is possible that this may relate to a pressor response resulting from water intake, rather than from a volume effect.<sup>112,113</sup> In another small study of older adults, investigators observed an SBP increase of 12 mmHg and a 56% response rate (SBP increase  $\geq$ 10 mmHg) in response to water intake, which was similar to abdominal compression but greater than with either physical countermeasures or compression stockings.<sup>114</sup> In contrast, a distinct study of older adults with OH found no

benefit in the SBP response rate when combining physical countermeasures with and without abdominal compression and water bolusing (480 mL room temperature tap water). However, there was a suggestion that the combination of all 3 might enhance the SBP response among those who did respond. However, these combinations did not improve symptoms.<sup>115</sup> Additional research is needed in larger patient populations before this approach can be adapted more widely in clinical practice. Nevertheless, water bolusing may possibly be the most readily available intervention in those with OH without swallowing difficulties or gastric emptying problems.

#### 4. Pharmacological treatment of OH for specific conditions

a. Neurogenic OH. Although nonpharmacological approaches are first steps for OH in general, adults with symptomatic neurogenic OH may benefit from treatment. Thus, a stepwise approach is recommended. Medications should be used only if conservative measures fail, but medications are often needed in patients with moderate to severe neurogenic OH. Only 2 medications are approved for the treatment of OH: midodrine and droxidopa. All others are used off-label. Ideally, therapies for OH in the patient with hypertension would selectively improve upright BP without increasing supine BP. Most pressor agents used in OH, however, increase both supine and upright BPs, and some increase supine BP more than standing BP.

Fludrocortisone is an example of the latter. It is a synthetic mineralocorticoid frequently added to increase the efficacy of salt supplementation to promote sodium retention, transiently expand plasma volume, and enhance the pressor effect of norepinephrine to increase peripheral vascular resistance.<sup>116</sup> A pharmaco-epidemiological study found higher rates of all-cause hospitalizations in fludrocortisone users compared with midodrine users, especially among patients with congestive heart failure.<sup>117</sup> Therefore, fludrocortisone is contraindicated in the presence of heart failure, a common comorbidity in patients with OH, and should be used with caution, if at all, in patients with supine hypertension. Overall evidence in support of fludrocortisone is weak.<sup>116</sup>

Midodrine is an oral  $\alpha$ -1 adrenergic receptor agonist shown in 2 randomized clinical trials to be effective in increasing upright BP.<sup>118,119</sup> However, it also produces a greater increase in supine than standing BP, and its label includes a black-box warning about worsening supine BP.

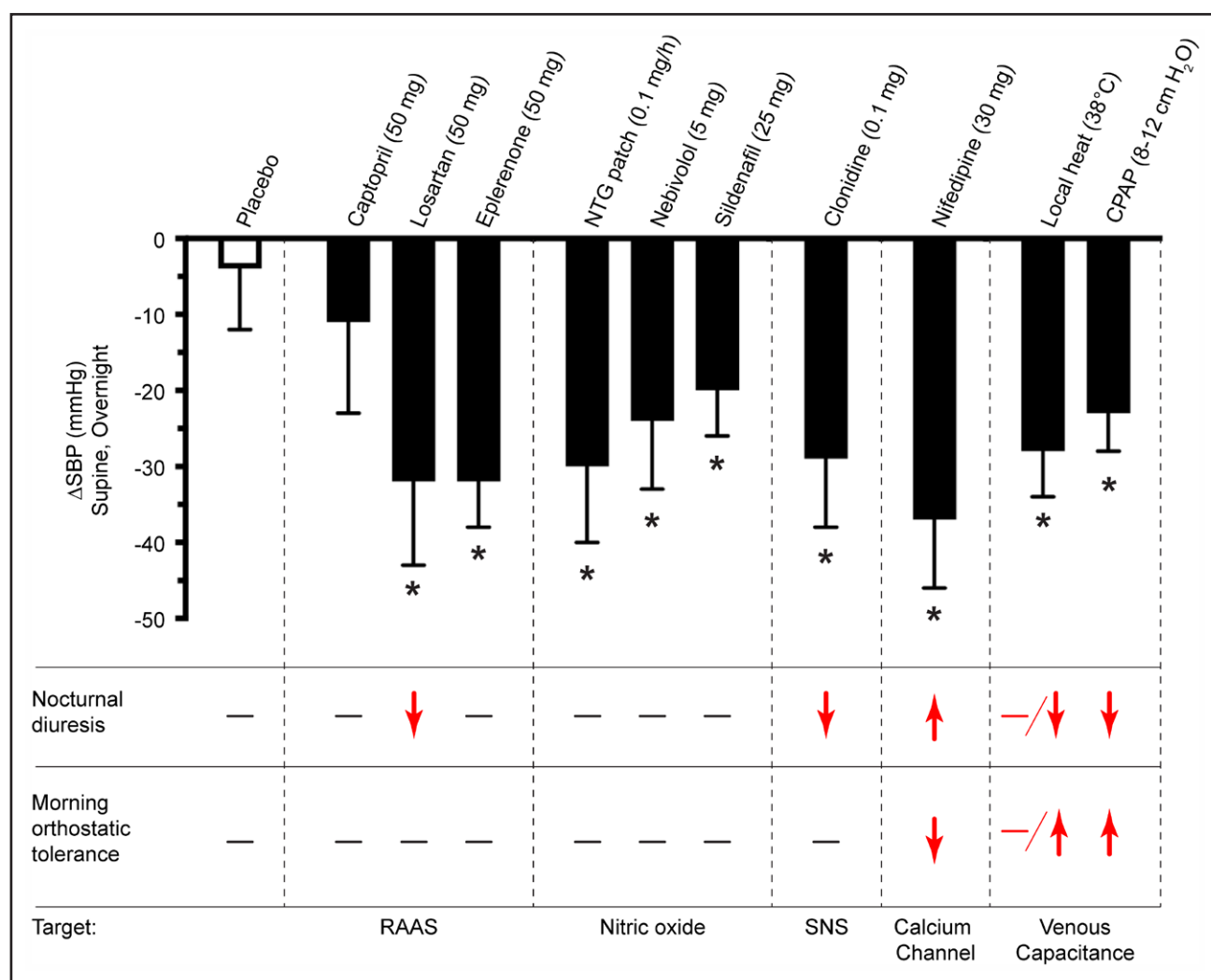
Droxidopa is a prodrug that is converted into norepinephrine by dopa decarboxylase,

the enzyme that also converts levodopa into dopamine.<sup>120</sup> It was approved for the treatment of neurogenic OH on the basis of 3 randomized clinical trials demonstrating improvement in OH symptoms.<sup>121–123</sup> Supine hypertension is the most common side effect of droxidopa but with a low rate ( $\leq 7.9\%$  versus  $\leq 4.6\%$  for placebo),<sup>124</sup> and droxidopa is considered safer than midodrine in this regard. A recent meta-analysis found that midodrine, but not droxidopa, significantly increases risk for supine hypertension.<sup>125</sup>

Arguably the safest drug to use in patients with OH and hypertension is pyridostigmine, an acetylcholinesterase inhibitor that enhances cholinergic neurotransmission at the level of the autonomic ganglia, thereby increasing both sympathetic and parasympathetic activity. The appeal of this pharmacological approach is that it is engaged only during the sympathetic activation that occurs while upright to selectively increase upright BP without worsening supine hypertension.<sup>126,127</sup> These studies, however, involved small numbers of patients and found only small improvements in upright SBP (4 mmHg compared with placebo). Pyridostigmine may not be effective in severely affected patients.<sup>128</sup>

b. Isolated supine hypertension in patients with severe neurogenic OH. The clinical picture of patients with neurodegenerative disorders of the autonomic nervous system is dominated by disabling OH and isolated supine hypertension. This can be due to preexisting hypertension or can occur de novo as part of their impaired autonomic regulation of BP. Most patients with normal seated BP and daytime supine hypertension can be managed by simply avoiding the supine position during the day. Nocturnal (supine) hypertension remains the main problem. Two-thirds of patients with neurogenic OH have a nondipping or reverse dipping pattern, and nocturia induces pressure natriuresis (average nighttime loss of 1.3 L of water and 70 mmol of sodium), leading to volume depletion and worsening of daytime OH.<sup>129</sup> The ideal treatment would control nocturnal hypertension, reduce natriuresis, and improve daytime (or at least early-morning) OH. Nighttime hypertension can be effectively controlled with several short-acting antihypertensives given at bedtime, including nitroglycerin patch (removed in the morning), sildenafil, clonidine, nebivolol (but not metoprolol),<sup>130</sup> immediate-release nifedipine, losartan, and eplerenone. Of these, only losartan reduces nighttime natriuresis, and none improve daytime OH (Figure 4).<sup>133</sup> Notably, losartan but not captopril lowers supine BPs in patients with severe





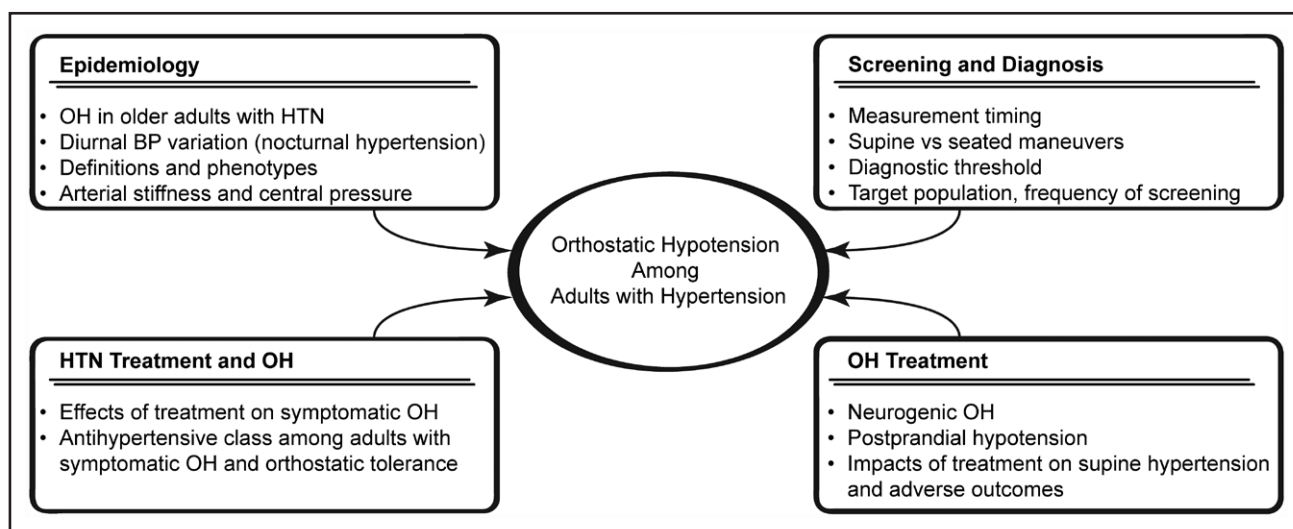
**Figure 4. Effect of different antihypertensive medications and nonpharmacological interventions on nocturnal hypertension, diuresis, and morning orthostatic tolerance in patients with supine hypertension and OH.** Interventions were tested on a series of single-night, placebo-controlled crossover, proof-of-concept studies.<sup>131,132</sup> Outcomes were monitored from 8 PM to 8 AM, followed by a 10-minute standing test in the morning. A single oral dose of each medication was given at 8 PM; nitroglycerin (NTG) patch was applied from 8 PM to 6 AM; and local heat and continuous positive airway pressure (CPAP) were applied from 10 PM to 6 AM. Vertical bar represents the maximum observed systolic blood pressure (SBP) reduction over night. Asterisk represents interventions that significantly reduced nighttime SBP. Only local heat and CPAP treatment reduce nocturnal diuresis and improve morning orthostatic tolerance. Red indicates the observed effect. Nifedipine here is the immediate-release formulation. OH indicates orthostatic hypotension; RAAS, renin-angiotensin-aldosterone system; and SNS, sympathetic nervous system. Figure courtesy of Luis E. Okamoto, Vanderbilt University Medical Center. Adapted with permission from Park et al.<sup>133</sup> Copyright © 2022 Springer Nature.

autonomic failure, suggesting extrarenal generation of angiotensin II in these patients.<sup>134,135</sup>

In contrast, small proof-of-concept clinical studies have shown that sleeping in a head-up tilt position, application of local passive heat (water-recirculating heated mattress), and continuous positive airway pressure (at levels used in sleep apnea) control nocturnal hypertension (as effectively as antihypertensives), reduce nocturia, and improve early-morning OH (Figure 4).<sup>131,132</sup> Unfortunately, to be effective, sleeping in a head-up tilt position requires levels of tilt of at least 12° (≈16-in elevation of the

head of the bed), which is not practical, tolerable, or safe. Both local heat and continuous positive airway pressure reduce cardiac output by increasing venous capacitance through skin vasodilation or splanchnic venous pooling, respectively. The magnitude of the BP-lowering effect (≈30 mmHg) is similar to that seen with antihypertensive agents<sup>133</sup> but has been documented only in patients with severe impairment of compensatory autonomic reflexes.

c. Hypertension with intermittent hypotensive events. These patients are characterized as having hypertension but have periods of often



**Figure 5. Summary of research priorities for OH among adults with hypertension.** BP indicates blood pressure; HTN, hypertension; and OH, orthostatic hypotension.

symptomatic drops in BP. Common but often underrecognized examples are postprandial hypotension and postexercise hypotension (see Supplemental Material SM1 for details). In these patients, ambulatory BP monitoring is particularly useful to characterize the mean awake-time BP, the severity of hypotensive events (including any symptoms, sequelae, or signs of end-organ damage), and the frequency of hypotensive events. These data can inform treatment strategies focused on augmenting or reducing BP to minimize the effects of BP lability. In cases of refractory hypertension, particularly when baroreflex impairment is thought to be the primary cause, guanfacine or clonidine patches have been useful.<sup>136,137</sup>

## CONCLUSIONS

OH is common among adults with hypertension and increases with age as a result of impairments in autonomic reflex. Although a more aggressive hypertension treatment goal may lower the risk of OH, particularly with first-line antihypertensive agents, some second-line classes of antihypertensive agents may cause OH, and monitoring for OH may be beneficial in older patients with the initiation of new treatments. When OH is identified or in the setting of orthostatic symptoms, characterizing OH and establishing its cause are important first steps. Nonpharmacological interventions are first-line treatments regardless of cause, but modification of antihypertensive regimen and addition of medications to treat OH should take into account the cause of OH, comorbid hypertension, and cardiovascular disease risk.

Ultimately, substantially more research is needed to understand and treat this form of BP dysregulation. A number of areas representing research priorities for OH are summarized in Figure 5 (Supplemental Material SM2 provides details).

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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\*Modest.

†Significant.

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\*Significant.

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