

REVIEW TOPIC OF THE WEEK

# Orthostatic Hypotension

## Epidemiology, Prognosis, and Treatment



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### ABSTRACT

Orthostatic hypotension (OH) is a common cardiovascular disorder, with or without signs of underlying neurodegenerative disease. OH is diagnosed on the basis of an orthostatic challenge and implies a persistent systolic/diastolic blood pressure decrease of at least 20/10 mm Hg upon standing. Its prevalence is age dependent, ranging from 5% in patients <50 years of age to 30% in those >70 years of age. OH may complicate treatment of hypertension, heart failure, and coronary heart disease; cause disabling symptoms, faints, and traumatic injuries; and substantially reduce quality of life. Despite being largely asymptomatic or with minimal symptoms, the presence of OH independently increases mortality and the incidence of myocardial infarction, stroke, heart failure, and atrial fibrillation. In this review, we outline the etiology and prevalence of OH in the general population, summarize its relationship with morbidity and mortality, propose a diagnostic and therapeutic algorithm, and delineate current challenges and future perspectives.

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Orthostatic hypotension (OH) is a key manifestation of autonomic dysfunction, typically observed when cardiovascular adaptive mechanisms fail to compensate for the reduction in venous return that normally occurs on assuming the upright position. It reflects a structural or functional sympathetic denervation or a deranged reflex regulation of sympathetic outflow (1). OH is the second most common etiology of syncope, occurring in approximately 15% of syncope presentations (2). It frequently affects older people and patients who have neurodegenerative disease, diabetes, or hypertension. Unfortunately, OH is often unrecognized or misdiagnosed and may be an overlooked factor associated with increased cardiovascular morbidity and all-cause mortality. Its management includes both pharmacological and nonpharmacological measures that are not always satisfactory and may lead to complications (3). In this review, we first outline the pathophysiology of OH; discuss its etiology,

epidemiology, and prognosis; and propose a diagnostic and therapeutic algorithm.

### THE HOMEOSTATIC REGULATION OF BLOOD PRESSURE

Cardiovascular blood pressure (BP) homeostasis refers to compensatory adjustments aimed at buffering changes in BP and opposing cardiovascular remodeling. Regulation of BP is a very complex physiological function that depends on a continuum of actions of the cardiovascular, neural, renal, and endocrine systems (4). In contrast to the local (peripheral) regulation of tissue BP, which primarily aims to achieve a tight matching of regional blood flow to local metabolic demands and occurs through locally produced mediators (autacoids), including eicosanoids, nitric oxide, endothelins, and tissue plasminogen activator, the central circulation maintains tight control of BP through changes in cardiac output and vascular tone.



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Such changes are mediated by the autonomic nervous system. The sympathetic and parasympathetic components of the autonomic nervous system play a crucial role in the fine-tuning of BP, enabling the body to respond to physiological stressors. The sympathetic nervous system plays the predominant role in determining the level of arterial BP and the distribution of cardiac output. Despite the existence of cholinergic vasodilation in some vascular beds, the overall contribution of the parasympathetic nervous system to the regulation of vascular tone is almost negligible, in contrast to the role of the parasympathetic nervous system in the regulation of cardiac functions via its negative chronotropic and inotropic effects.

Central regulatory mechanisms control the sympathetic outflow to the cardiovascular system in both the short and long term (5). Short-term reflex control of the sympathetic vasomotor activity is regulated by homeostatic feedback mechanisms, such as the baroreceptor and chemoreceptor reflexes. Central mechanisms also produce specific patterns of sympathetic activity according to different external stimuli or stresses (6,7). In the long term, cardiovascular homeostasis depends on a more complex interplay of several mechanisms, including changes in the sympathetic vasomotor outflow, renal control of extracellular volume, pressure natriuresis, and the activity of antagonistic “push-pull” systems (8), such as the kallikrein-kinin and renin-angiotensin-aldosterone systems (5,6,9–12).

**PHYSIOLOGY OF UPRIGHT POSTURE.** Orthostatic stress is a common daily challenge for humans when posture changes from lying to standing or during prolonged quiet standing. Almost immediately, with the transition from the supine (recumbent) to the upright (erect) position, a gravitational shift of nearly 500 ml of blood away from the chest to the distensible venous capacitance system below the diaphragm (venous pooling) occurs. This results in a rapid decrease in central blood volume and a subsequent reduction of ventricular preload, stroke volume, and mean BP (13). In the vascular system, a reference quantitative determinant of these changes is the venous hydrostatic indifference point (HIP), when pressure is independent of posture (14). In humans, the venous HIP is approximately at the diaphragmatic level, whereas the arterial HIP lies close to the level of the left ventricle (14). The venous HIP is dynamic and is significantly affected by venous compliance and muscular activity.

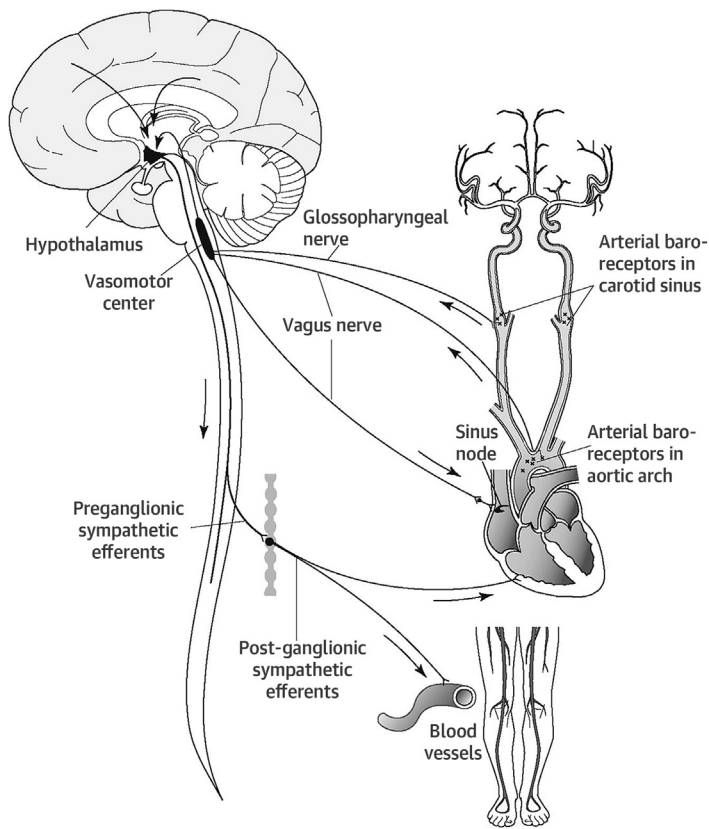
Upon standing, contractions of lower limb muscles, along with the presence of venous valves, provide an intermittent unidirectional flow, moving the venous HIP toward the right atrium (15). Respiration

may also increase venous return because deep inspiration results in both a decline in thoracic pressure and an increase in intra-abdominal pressure, which lowers retrograde flow due to compression of both the iliac and femoral veins (14). To provide an appropriate perfusion pressure to critical organs, an effective set of the neural regulatory system is promptly activated upon standing (6). The sympathetic nervous system is fast acting and primarily modulated by mechanoreceptors and, to a smaller degree, by chemoreceptors. Arterial baroreceptors (high-pressure receptors) are located in the carotid sinus and the aortic arch and—by conveying baroreceptive impulses via carotid sinus and aortic depressor nerves to the brainstem, notably in the nucleus of the solitary tract—determine tonic inhibition of vasomotor centers (16) (Figure 1). In contrast, cardiopulmonary baroreceptors (volume receptors) are located in the great veins and the cardiac chambers and detect changes in the filling of the central venous circulation but are not essential for orthostatic cardiovascular homeostasis (16). A sudden drop in BP in the carotid sinus and the aortic arch triggers baroreceptor-mediated compensatory mechanisms within seconds, resulting in increased heart rate, myocardial contractility, and peripheral vasoconstriction (17). An additional local axon reflex, the veno-arteriolar axon reflex, results in constriction of arterial flow to the muscles, skin, and adipose tissue, leading to almost one-half of the increase in vascular resistance in the limbs upon standing (14,18,19). Ultimately, orthostatic stabilization is normally achieved in roughly 1 min or less. During prolonged quiet standing, in addition to venous pooling, transcapillary filtration in the subdiaphragmatic space further reduces both central blood volume and cardiac output by approximately 15% to 20% (20,21). This transcapillary shift equilibrates after approximately 30 min of upright posture, which can result in a net fall in plasma volume of up to 10% over this time. Continued upright posture also results in activation of neuroendocrine mechanisms, such as the renin-angiotensin-aldosterone system, which may vary in intensity depending on the volume status of the patient (18). Still, the most important homeostatic response to prolonged orthostatic stress appears to be the carotid baroreflex-mediated increase of peripheral vascular resistance. The inability of any one of these factors to perform adequately or coordinately may result in a failure of the system to compensate for an initial or sustained postural challenge. This may produce a transient or persistent state of hypotension, which, in turn, can lead to

## ABBREVIATIONS AND ACRONYMS

<b>BP</b>	= blood pressure
<b>ECG</b>	= electrocardiogram
<b>HIP</b>	= hydrostatic indifference point
<b>HUT</b>	= head-up tilt test
<b>OH</b>	= orthostatic hypotension
<b>SBP</b>	= systolic blood pressure

**FIGURE 1 Baroreceptor-Mediated Regulation of Blood Pressure**



The afferent pathway transfers information from arterial baroreceptors in the carotid artery and the aortic arch. This information reaches the vasomotor center in the medulla oblongata. The efferent pathway regulates 2 basic cardiovascular responses: heart rate and vascular tone. The hypothalamus can then activate vasopressin release as additional regulatory mechanisms. Higher brain functions can modulate automatic cardiovascular responses.

symptomatic cerebral hypoperfusion and loss of consciousness, either in the early or late phase of orthostatic challenge (3).

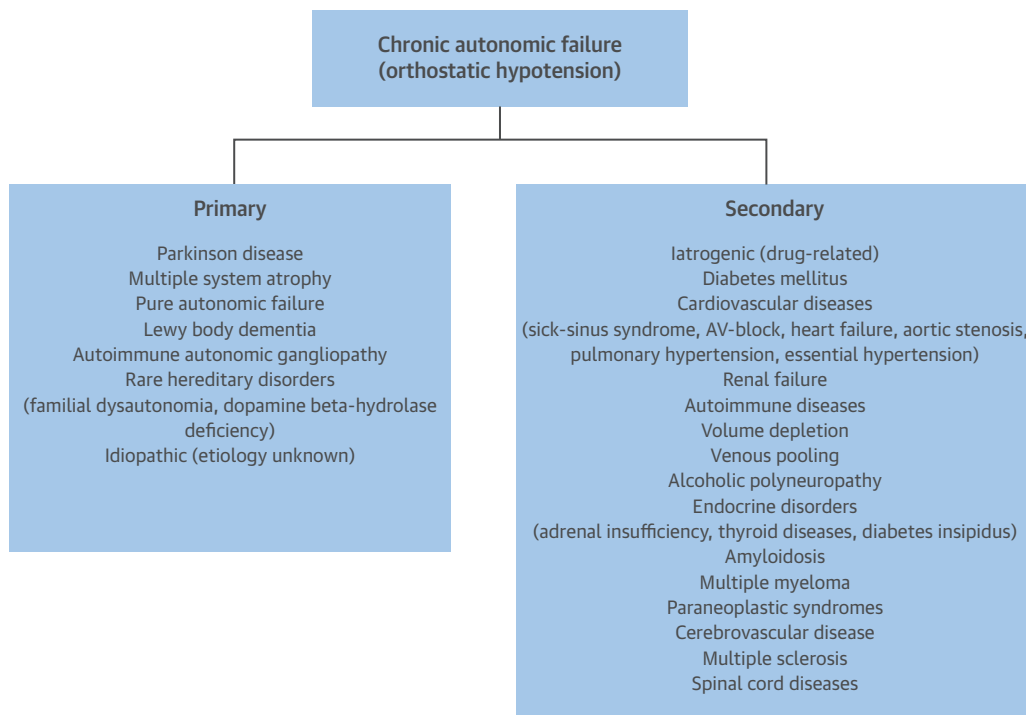
**ORTHOSTATIC INTOLERANCE SYNDROMES: DEFINITIONS, ETIOLOGIES, AND TYPICAL FORMS.** Orthostatic intolerance defines the inability to tolerate the upright posture as a consequence of varying degrees of autonomic nervous system dysfunction (22). A number of different disorders of orthostatic control have been identified that are unique in many ways, although they share certain characteristics (14). According to the 2011 updated consensus statement endorsed by major international autonomic nervous system and neurological societies and in agreement with the European Society of Cardiology, orthostatic intolerance syndromes can be classified into at least 3 categories: 1) orthostatic hypotension; 2) neutrally

mediated (reflex) syncope; and 3) postural tachycardia syndrome (23,24). Both reflex syncope and postural orthostatic tachycardia syndrome have been discussed in detail elsewhere (22,25-27).

OH can be classified as either primary or secondary (1) and can be further subdivided into acute and chronic forms (18) (Figure 2). On a pathophysiological basis, OH may be divided into 2 broad categories dealing with structural (neurogenic) or functional (or non-neurogenic) causes of autonomic nervous system failure. Neurogenic OH is a key manifestation of chronic autonomic failure in primary neurodegenerative disorders, such as pure autonomic failure, multiple system atrophy, or Parkinson disease, but can also be secondary to neurological diatheses associated with diabetes, amyloidosis, or advanced renal failure (3). Factors that may cause functional impairment of the autonomic nervous system include treatment with vasodilators, tricyclic antidepressants, diuretics, or chemotherapeutic agents; absolute or relative reduction in circulating blood volume; venous pooling; and inotropic and/or chronotropic heart failure (28,29).

OH may provoke signs and symptoms of cerebral hypoperfusion, including nausea, fatigue, lightheadedness, dizziness, "coat-hanger" pain, visual blurring, and eventually syncope. Whether or not the patient experiences symptoms is as much dependent on the rate of the decrease in pressure as it is upon the absolute degree of change. Most patients with OH are asymptomatic or have few nonspecific symptoms, thus accounting for the high rate of unrecognized cases. Patients with OH may also suffer from supine hypertension, as well as wide swings in BP, or may experience abnormal responses to a number of pharmacological or physiological challenges (14,18). Symptoms are more common and more severe in the morning and after waking and are typically exacerbated by conditions predisposing to peripheral venous pooling and dehydration, such as heat, fever, alcohol drinking, urination, post-exercise time, and immobilization. Also, patients with autonomic failure are more susceptible to post-prandial hypotension, especially when consuming large meals and carbohydrate-rich food, due to gastric distension, release of vasodilatory peptides, and splanchnic blood pooling (30). Interestingly, a common complaint is nocturnal polyuria, which is the result of redistribution of peripheral blood to central areas while in the recumbent position and is further exacerbated by forced natriuresis with concomitant supine hypertension. Hence, these patients may suffer significant intravascular volume loss overnight, enhancing the tendency toward morning hypotension.

**FIGURE 2** Etiology of Primary and Secondary Chronic Autonomic Failure With Symptoms of Orthostatic Hypotension



Orthostatic hypotension caused by primary disease of the autonomic nervous system (**left panel**) is often referred to as neurogenic orthostatic hypotension. AV = atrioventricular.

On the basis of temporal changes in orthostatic BP, 3 different clinical variants of OH have been proposed: classic, delayed, and initial OH.

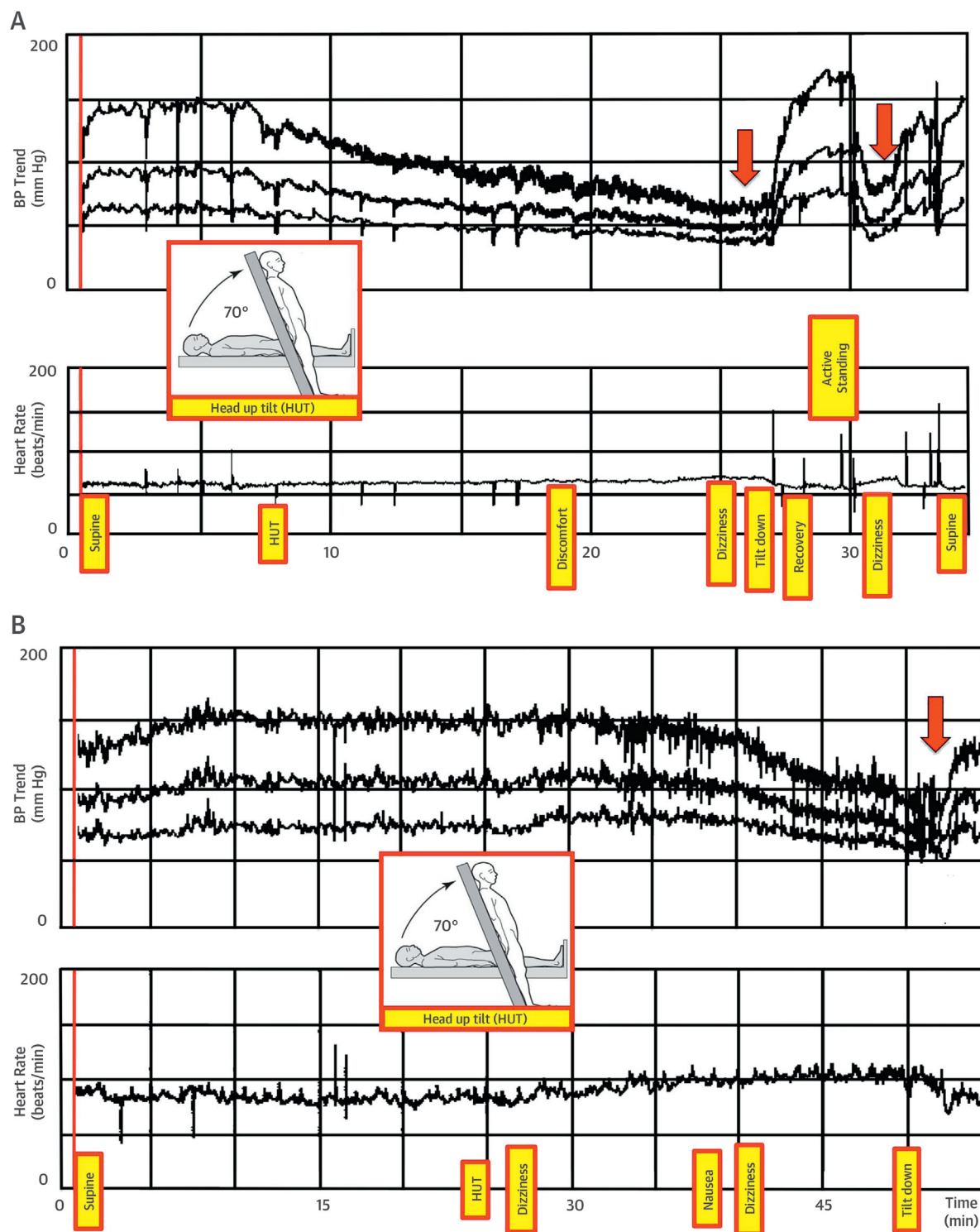
**Classic OH.** Classic OH (**Figure 3A**) is defined as a sustained reduction in systolic BP (SBP) of at least 20 mm Hg and/or diastolic BP of at least 10 mm Hg, within 30 to 180 s of active standing or during a head-up tilt test of at least 60° (24). In patients with supine hypertension, a reduction in systolic BP of at least 30 mm Hg is considered to be a more appropriate criterion for OH because the magnitude of the BP decrease is proportional to baseline values (24). Although closely related to neurogenic OH, classic OH rarely features symptoms of generalized autonomic failure (1,3,28), and after extensive neurological evaluation, approximately one-third of patients have no identifiable etiology (29).

In many cases when the structural autonomic disease cannot be confirmed, the term idiopathic OH has been widely used (29). Recent data indicate that autoimmune activity against adrenergic and muscarinic receptors may be responsible for exaggerated vasodilation and symptoms of OH in the idiopathic form, but further studies are needed (31). It should be

emphasized that the diagnostic rate of neurogenic OH may differ between specialized neurological centers and cardiology-focused syncope units, with higher rates of neurodegenerative disorders expected in the former. Nonetheless, classic OH constitutes a key and typical manifestation of sympathetic neurocirculatory failure (32), causing impaired chronotropic and vascular responses during early orthostasis.

**Delayed OH.** Delayed OH (**Figure 3B**) is due to gradual impairment of adaptive mechanisms during orthostasis, resulting in a slow progressive drop in arterial pressure (BP decrease  $\geq 20/10$  mm Hg or  $\geq 30/15$  mm Hg in patients with hypertension) between 3 and 45 min. It has been associated with milder abnormalities of sympathetic adrenergic function, suggesting that this disorder may be a less severe or an early form of autonomic failure, along with age-related impairment of compensatory reflexes and with a stiffer, more pre-load-dependent heart in older patients (23,33). The absence of bradycardia or pauses usually differentiates delayed OH from reflex syncope, although mixed forms are often encountered in clinical practice.

**FIGURE 3** Tracings During a Head-Up Tilt Test Performed in 2 Prototypical Patients With Unexplained Transient Loss of Consciousness



The upper tracing in each panel shows a beat-to-beat blood pressure (BP) measurement and consecutive test stages. The lower tracing shows the heart rate. **Red arrows** mark the moment when syncope occurs. **(A)** A 52-year-old woman with classic orthostatic hypotension and reflex syncope during passive head-up tilt (HUT). **(B)** A 74-year-old woman with delayed orthostatic hypotension and syncope during passive HUT.

**Initial OH.** In contrast to the classic and delayed forms, initial OH is defined as a transient BP decrease (SBP decrease  $>40$  mm Hg and/or diastolic BP decrease  $>20$  mm Hg) within 30 s of standing (3). This may be an unrecognized cause of syncope (34) and is related to an exaggerated and immediate transient decrease in arterial BP upon standing. It is exclusively associated with active standing, whereas the drop in BP during passive tilting is significantly smaller, or, in many cases, totally absent. The mechanism of initial OH involves a short-lasting mismatch between a sudden decrease in venous return and neurally mediated compensatory vasoconstriction. The diagnosis of initial OH is quite challenging and can only be confirmed by an active standing test with continuous BP monitoring.

#### EPIDEMIOLOGICAL AND PROGNOSTIC ASPECTS OF OH.

OH has been traditionally associated with neurodegenerative diseases (1), frailty in elderly patients (35), and chronic heart failure (36), but it is also a frequent finding among patients with hypertension (37,38) and patients with diabetes (39). In published reports, its prevalence ranges between 6% and 35% or more, depending on age and associated comorbidities, showing a strong association with elevated BP (37,38,40,41). In many chronic conditions, such as renal failure or autoimmune diseases, OH has a higher prevalence than in the general population, suggesting the multifactorial etiology of autonomic failure. There is now growing evidence that disorders of postural hemodynamic control predict all-cause mortality (42-44) and incidence of cardiovascular disease (44,45), being prognostically more relevant than the ambulatory BP monitoring-derived nighttime reverse dipping (46). According to the available longitudinal data, OH is associated with increased risk of major adverse cerebrocardiovascular events, although results have not always been consistent (43,47,48). Nonetheless, a recent meta-analysis of prospective observational studies confirmed that the presence of OH was independently associated with increased risk of all-cause death, incident coronary heart disease, heart failure, and stroke (49). Unexpectedly, post-hoc subgroup analysis documented a stronger association between OH and mortality in the population  $<65$  years of age, whereas such association barely attained full statistical significance in the older subgroup (49). Similar discrepancies were also observed in the ARIC (Atherosclerosis Risk in Communities) study (50,51) and in the Cardiovascular Health Study (52), in which the relative risk of stroke predicted by OH decreased with advancing age. Prospective data of the Swedish Malmö Preventive Project showed a 2-fold higher risk of death in individuals

with OH  $<42$  years of age, strongly supporting a causal relationship between OH and increased all-cause mortality. An appreciation of the plausibility of a pathophysiological link between the OH status and negative outcomes, such as death and cerebrocardiovascular events, requires several considerations. Higher diurnal BP variability and supine (nocturnal) hypertension, both present in OH, may provoke intermittent bouts of increased afterload, leading to permanent end-organ damage, such as left ventricular hypertrophy and decreased renal function, thereby paving the way to left ventricular diastolic dysfunction, increased risk of congestive heart failure, and myocardial ischemia. Furthermore, altered autonomic tone in patients with sleep apnea (53) and hypertension (54) is known to be associated with the occurrence of atrial fibrillation (55,56), which is itself a well-known risk factor for heart failure (57) and cardioembolic stroke (58). Fedorowski *et al.* (59) observed that, independent of conventional risk factors, the long-term incidence of atrial fibrillation was significantly higher among individuals with hypertension and OH, further strengthening the link between autonomic dysfunction and cardiovascular morbidity. Impaired orthostatic homeostasis is responsible for the activation of neuroendocrine compensatory mechanisms, which may themselves trigger the activation of other biological effectors (e.g., platelets or the coagulation cascade), potentially promoting the occurrence of cardiovascular or cerebrovascular events. Corroborating this hypothesis, hyperactivation of the endothelin system has been observed in patients diagnosed with syncope due to OH (60). Thus, physiological vasoconstrictors, such as endothelin 1 and vasopressin, which play an important role in adaptive mechanisms during prolonged orthostatic stress, may promote atherothrombotic events in susceptible individuals, when chronically upregulated (61). However, current knowledge does not allow us to draw any firm conclusion as to whether OH is a marker of a generally increased risk of death, an intermediate variable in the causal pathway of cardiovascular risk factors, a simple measure of disease severity, or an independently acting mechanism. Thus, assessment of OH in prospective epidemiological studies should be encouraged. Moreover, future randomized trials in chronic cardiovascular diseases, such as hypertension, ischemic heart disease, and heart failure, should explore how prevalent OH influences study outcomes, and whether bedtime intake of antihypertensive drugs, aimed at restoring the nighttime dipping pattern (62,63), can improve prognosis in patients with the supine hypertension-OH syndrome (64).

**DIAGNOSIS.** OH is diagnosed on the basis of a simple principle: to demonstrate a significant persistent BP decrease during orthostasis, either by the bedside active-standing test or using a more sophisticated head-up tilting test. The latter test is, however, not always available and usually warrants interpretation by a well-trained expert. The tests are usually performed when the clinical scenario is suggestive of OH, such as in the presence of characteristic postural symptoms, unexplained syncope, or fall injury. However, population-based epidemiological studies have shown that OH is common in asymptomatic individuals (45,65) and may be accidentally found during screening or routine clinical investigation (66–69). Taking into account that OH prevalence is strongly age dependent and up to one-third of patients >70 years of age may have it (66), we propose that the bedside orthostatic test be routinely performed in this age group, whereas patients <70 years of age should probably undergo the orthostatic test only if clinical signs suggestive of OH are present (Figure 4). Apart from the orthostatic BP test, the initial assessment of patients with suspected OH may be complemented by standard cardiac and neurological tests, according to past medical history; results of the physical examination; and an electrocardiogram (ECG). An expert in cardiovascular dysautonomia should be responsible for the next stage in OH evaluation, having mandatory access to the head-up tilt test and other autonomic tests, as well as to prolonged BP and ECG monitoring (Figure 4). However, lack of real experts, both in numbers and local accessibility, has always been an important limitation in the implementation of such schemes. Traditionally, specialists in either cardiology or neurology have been involved in OH diagnostics at an advanced level. Although the former are primarily oriented toward the cardiovascular consequences of OH, such as syncope, hypotension versus hypertension, and unexplained falls in older patients (23,40,70), the latter predominantly focus upon the structural and functional changes in the autonomic nervous system, including cardiac autonomic imaging and neuroendocrine tests (28,29,71). Nevertheless, establishing a higher number of centers with a trained and adequately equipped professional staff would be an important step toward optimal management of all patients with OH. When properly diagnosed, patients with OH may need referral to other specialists (Figure 4), especially if the investigating unit lacks competence in specific areas such as neurodegenerative diseases, dementia, endocrinology, cardiac arrhythmias, or concomitant structural heart disease. In summary, symptomatic patients (class II to IV)

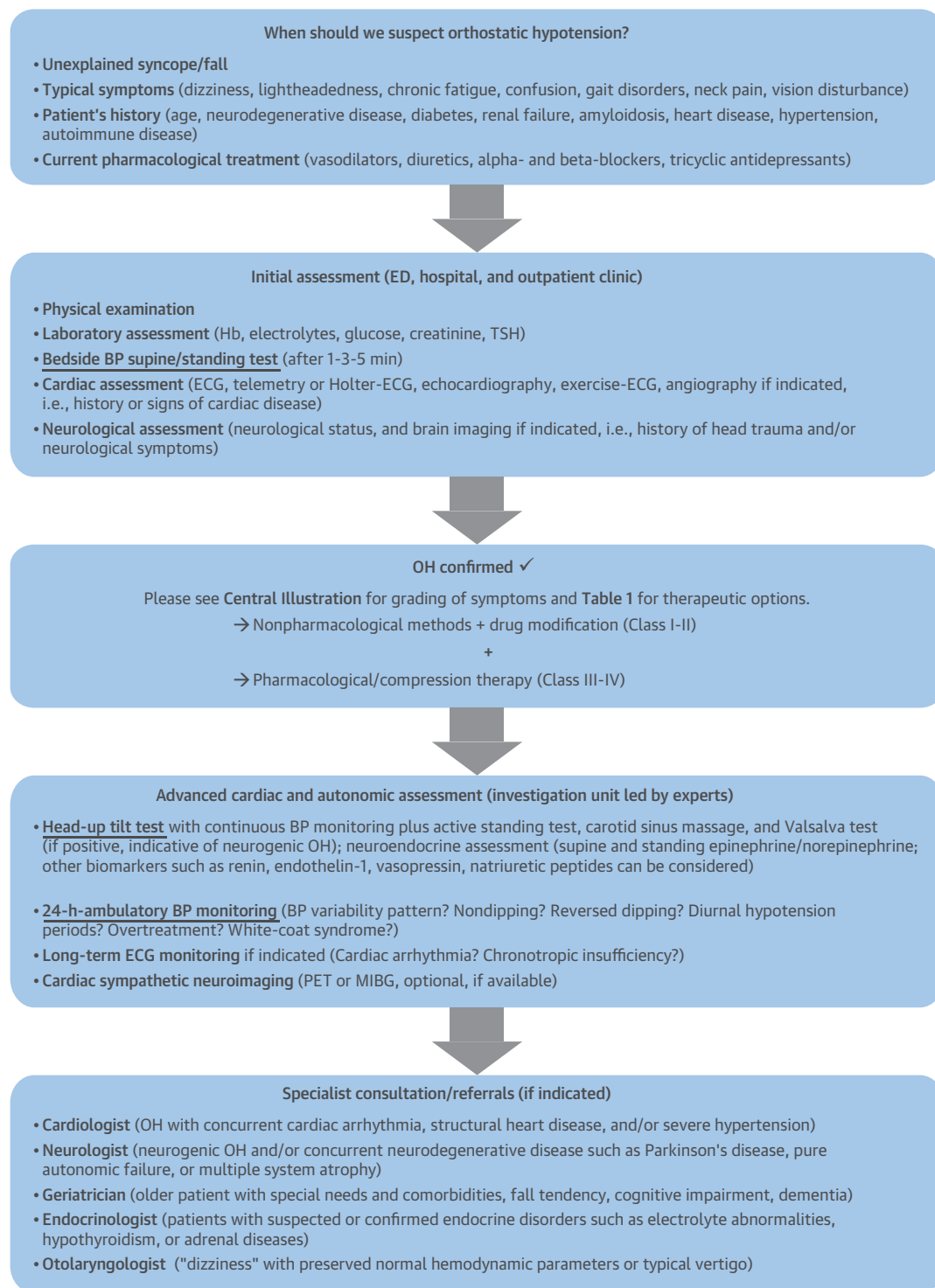
(Central Illustration) should undergo a more comprehensive investigation led by an expert in cardiovascular dysautonomia, using at least the head-up tilting test and 24-h ambulatory BP monitoring.

**TREATMENT.** The pivotal management of patients with OH starts with an evaluation of the severity and frequency of symptoms. Several useful grading tools are available (71). We present a modified symptom classification along with treatment recommendations. As shown in the Central Illustration, the prevalence of OH functional classes (I to IV) is inversely related to its severity, thus making asymptomatic OH the most prevalent form of this disorder.

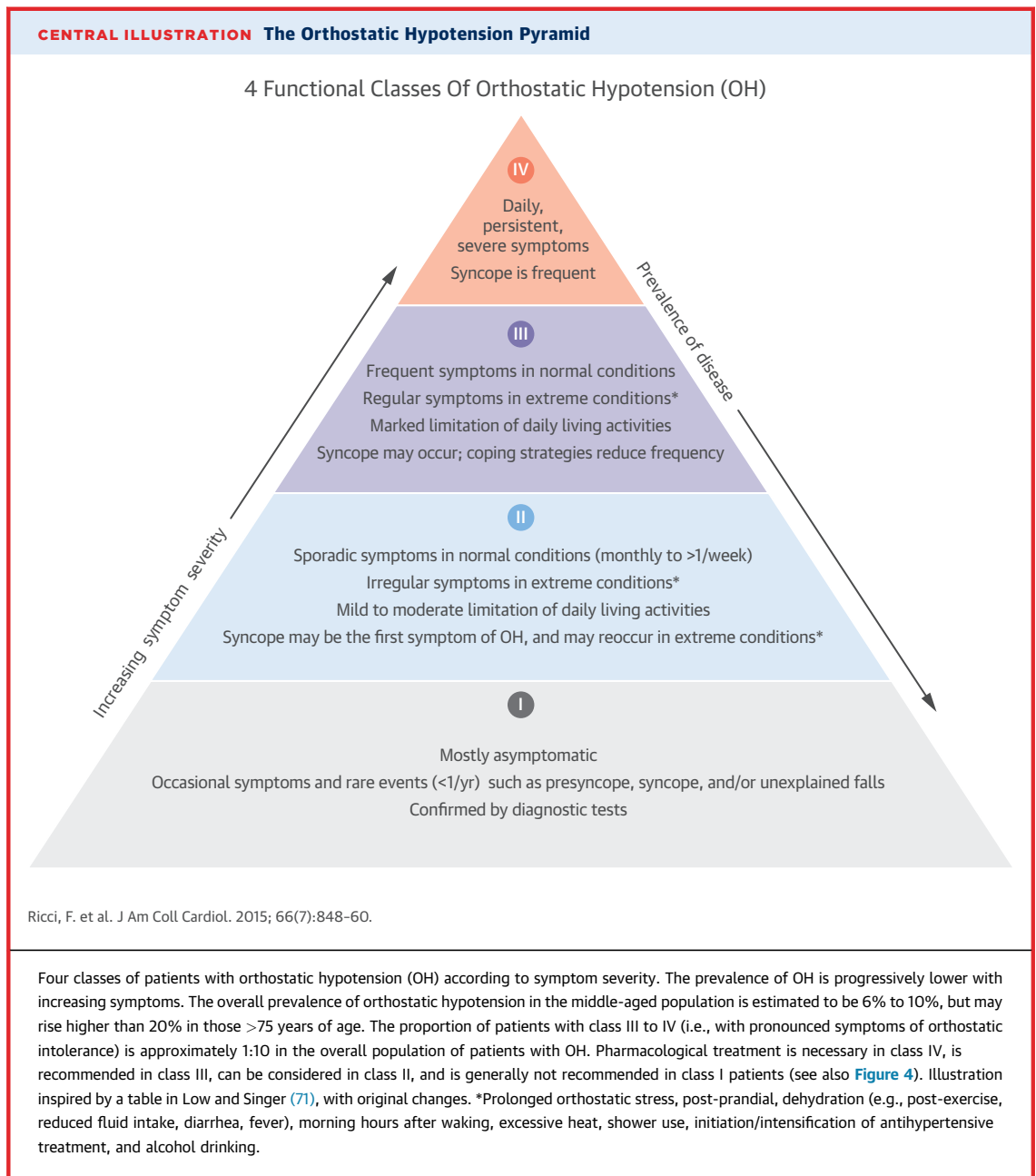
**Patient education.** Patient education is central to effective treatment of OH (Table 1). It is crucial that patients understand the basics of postural physiology and mechanisms of orthostatic intolerance, as well as aggravating factors; learn how to avoid conditions that potentially trigger symptoms and syncope; and be instructed in how to prevent BP decreases using physical countermeasures (72,73). When a patient is tested with continuous noninvasive BP monitoring, it is practical to perform a brief training session after the test to instruct the patient on how muscle tension and squatting can counteract BP decrease. Another important aspect of patient education, concomitant with a head-up tilting test, is proper recognition of warning signs in relation to hemodynamic changes. The efficacy of countermeasures in a critical situation depends on timely implementation, before irreversible circulatory collapse or vasovagal reflex activation occurs (Figure 3).

**Elastic stockings and abdominal binding.** When the symptoms of orthostatic intolerance are very pronounced (class III to IV) (Figure 4) and patient education plus pharmacological treatment does not lead to substantial improvement, and especially if the decrease in SBP to <90 mm Hg occurs shortly after standing and/or when signs of venous pooling are present, elastic stockings and abdominal binding may be helpful (Table 1) (74). Limb and abdomen compression improves orthostatic tolerance in up to 40% of symptomatic patients. The recommended compression pressure is 30 to 50 mm Hg for leg compression and 20 to 30 mm Hg for the abdomen. However, leg compression alone is not as effective as compression of the abdomen because the venous compartment of the lower limbs is smaller than that of the splanchnic region (75,76); therefore, “the higher, the better” principle should be applied. The main disadvantage of this method is that compression garments are inconvenient to put on and wear, particularly for older and disabled patients and during the summer season. However, the hemodynamic

**FIGURE 4** Proposed Algorithm for the Diagnosis and Management of OH



ECG = electrocardiography; ED = emergency department; Hb = hemoglobin; MIBG = meta-iodobenzylguanidine; OH = orthostatic hypotension; PET = positron emission tomography; TSH = thyroid-stimulating hormone; other abbreviations as in [Figure 3](#).



effects exerted by compression garments are immediate and easily recognized by the patient, and the method can be applied only when needed (i.e., when a prolonged orthostatic challenge is expected or planned).

**Pharmacological treatment.** Although nonpharmacological measures are effective, most patients with class III to IV orthostatic intolerance, experiencing severe, persistent, or very frequent symptoms, often immediately upon standing, require pharmacological treatment with antihypertensive drugs ([Table 1](#)). The efficacy of such pharmacological

therapy has been repeatedly questioned, and very few substances, including droxidopa and midodrine, have shown positive results in randomized trials ([77,78](#)), whereas small observational series have demonstrated some effects of midodrine additive to compression treatment ([79,80](#)). At present, droxidopa and midodrine are preferred and administered during the daytime to avoid nocturnal (supine) hypertension because both substances have favorable half-lives of approximately 3 h.

Droxidopa has been shown to improve orthostatic tolerance in patients with neurogenic OH, having an

**TABLE 1 Therapeutic Options in Symptomatic OH**

Therapeutic modality	Comments
<b>Nonpharmacological treatment</b>	
Education of patient <ul style="list-style-type: none"> <li>• Acceptance and understanding of orthostatic intolerance</li> <li>• Avoidance of immobilization, prolonged diurnal recumbence, and physical deconditioning</li> <li>• Gradual rising from supine and sitting positions, especially in the morning, after meals, and after urination/defecation</li> <li>• Small and frequent, rather than large, meals</li> <li>• Avoidance of prolonged standing and high environmental temperature and humidity (volume depletion)</li> <li>• Physical countermeasures (e.g., leg crossing, muscle tensing, squatting) during standing and prodromal symptoms</li> </ul>	This therapeutic modality is crucial and often underestimated but is rarely sufficient in pronounced orthostatic intolerance (class III-IV). Patients and their families should understand the basics of orthostatic physiology and the importance of nonpharmacological methods. Training with countermeasures and beat-to-beat monitoring of BP is recommended to increase patient compliance. Educational materials such as instructional films may be helpful.
Head elevation 10-30° during sleep	Reduction of nocturia, volume depletion, and supine hypertension.
Increased salt and fluid intake, including peroral water bolus, if needed	Volume expansion. Daily dietary intake of up to 10 g of sodium per day or salt tablets (e.g., 1 g 3 times per day) and fluid intake of at least 1.5 liters per day is recommended. A careful dosage regimen in heart and kidney failure should be followed.
Elastic stockings/abdominal binding	Reduction of peripheral pooling in the lower limbs and splanchnic region. Especially recommended for elderly patients.
<b>Pharmacological treatments</b>	
Midodrine (2.5-10 mg 2 or 3 times per day)	Direct $\alpha_1$ -adrenoreceptor agonist. One of the few pharmacological agents positively tested in placebo-controlled studies, but its efficacy has often been questioned.
Droxidopa (100-600 mg 3 times per day)	Norepinephrine precursor. Has been widely used off-label in severe OH. Recently approved by the FDA.
Pyridostigmine (30-60 mg 2 or 3 times per day)	Acetylcholinesterase inhibitor. Generally recommended for neurogenic OH only. BP increases marginally. Efficacy questioned.
Fludrocortisone (0.05-0.3 mg daily)	Mineralocorticoid. Volume expander. Increases sodium reabsorption and enhances sensitivity of $\alpha$ -adrenoreceptors. May worsen supine hypertension and hypokalemia.
Ephedrine/pseudoephedrine (25/30-50/60 mg 3 times per day)	Direct and indirect $\alpha_1$ -adrenoreceptor agonist. Efficacy controversial.
Desmopressin (nasal spray, 5-40 $\mu$ g daily; oral formulation, 100-800 $\mu$ g daily)	Vasopressin analogue. Volume expander. Increases water reabsorption and reduces nocturia. Efficacy uncertain.
Avoidance of antihypertensive drugs: nitrates, long-acting calcium channel blockers, and diuretics	Vasodilation and volume depletion. May worsen symptoms of orthostatic intolerance.
Withdrawal, dosage reduction, or bedtime administration of antihypertensive drugs (short-acting preferred)	Reversed BP dipping is common in OH. Assessment of 24-h BP profile is recommended to tailor antihypertensive therapy.
<b>Devices</b>	
Pacemakers/CRT	The role of pacemakers/CRT in OH is limited. However, if chronotropic insufficiency and/or left ventricle failure worsen OH symptoms, especially in elderly patients, device therapy may be considered.
BP = blood pressure; CRT = cardiac resynchronization therapy; FDA = U.S. Food and Drug Administration; OH = orthostatic hypotension.	

impact on both symptoms upon daily activities and standing SBP (increase by approximately 10 mm Hg) (77). However, its long-term efficacy is debatable. Droxidopa treatment is usually initiated at a dosage of 100 mg 3 times per day (upon waking in the morning, at midday, and in the late afternoon, at least 3 h prior to bedtime; e.g., at 7 AM, 1 PM, and 7 PM) and should be titrated until symptom reduction occurs in increments of 100 mg per 3 to 7 days to a maximum dose of 600 mg 3 times per day. Typical adverse effects include headache, dizziness, nausea, and aggravated hypertension and may occur in 5% to 10% of patients. If persistent, a dose reduction may be tested because adverse effects are often dose dependent.

Midodrine has demonstrated a low to moderate level of efficacy in OH, according to a recent meta-analysis (78). The drug has a positive impact on

orthostatic intolerance (observed in approximately 50% of treated patients) and has no serious adverse effects. On average, an increase in standing SBP of 10 to 15 mm Hg 1 h after drug administration has been observed. Nevertheless, some uncomfortable reactions (occurring in approximately 10% to 15% of patients), such as dysuria or piloerection (“goose bumps”) can be expected. Midodrine should be administered according to the same schedule as droxidopa, with a starting dose of 5 mg 3 times per day and a recommended dose of 10 mg 3 times per day.

Vasoactive treatment may be complemented by a volume expander, preferably fludrocortisone (81), due to its positive effect on  $\alpha$ -adrenergic receptor sensitivity. The usual starting dose is 0.1 mg once daily and should not exceed 0.3 mg. Typical adverse effects to observe in patients with OH are generalized

or localized edema, including pulmonary edema and ascites, as well as aggravated hypertension and hypokalemia. Thus, the use of fludrocortisone in patients with heart failure, kidney failure, or hypertension is contraindicated.

Another important aspect of pharmacological therapy in OH is related to cardiovascular comorbidities. Because several drugs used for treatment of ischemic heart disease, heart failure, cardiac arrhythmias, and hypertension may have a negative impact on postural homeostasis, tailored therapy is needed to avoid worsening of orthostatic symptoms (Table 1). In general, 24-h ambulatory BP monitoring should be performed first, and nighttime administration of short-acting antihypertensive drugs is preferred, even if the patient is treated for ischemic heart disease or heart failure. Drug classes to be avoided are presented in Table 1.

In choosing a specific drug, a peak effect time between 2 and 6 h and a half-life no longer than 12 h are important. Recommended classes are angiotensin-converting enzyme inhibitors (e.g., enalapril, ramipril, benazepril, or moexipril), angiotensin-receptor blockers (e.g., candesartan, losartan, valsartan, or eprosartan), and dihydropyridine calcium-channel blockers (e.g., felodipine, isradipine, or nifedipine) given once daily at least 3 h before bedtime. Daytime hypertensive episodes are of somewhat lesser importance (62), whereas sleep-time hypertension should be treated if BP is consistently higher than 160/90 mm Hg (82) in uncomplicated cases (i.e., symptomatic OH without concomitant target-organ damage) and preferably lower than 140/90 mm Hg in patients with a history of cerebrocardiovascular disease, diabetes, or renal failure (63). A reverse dipping pattern in combination with OH is particularly detrimental and indicates a more than doubled risk of

incident cardiovascular disease (46). Consequently, both the absolute reduction of nighttime BP and restoration of normal sleep-time dipping are crucial and can be easily monitored using repeated 24-h ambulatory BP monitoring and patient diaries. Furthermore, a reappraisal of the use of beta-blockers is warranted because these patients, especially those >70 years of age, often show signs of chronotropic incompetence (83). Additional tests (Holter ECG and exercise ECG testing) are recommended for decision-making. However, in the most severe cases, discontinuation of antihypertensive treatment may be the only solution if the patient remains symptomatic despite treatment modification.

## CONCLUSIONS

OH is a frequent condition in the general population, with a prevalence close to 6%, and the frequency increases with advancing age and comorbidities. Management of symptomatic OH consists of both nonpharmacological and pharmacological methods, but they are often unsatisfactory. Future studies should focus on elucidating mechanisms involved in neurodegenerative and non-neurodegenerative OH, test new and more effective therapies, and assess the impact of strategies aimed to prevent or treat OH on cardiovascular diseases.

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