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REVIEW ARTICLE

# Orthostatic hypotension in clinical practice: Definitions, pathophysiology, outcomes, and future directions

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## Abstract

Orthostatic hypotension (OH) is a common but underrecognized disorder defined by an abnormal fall in blood pressure on standing. It reflects impaired autonomic and cardiovascular adaptation to postural change, leading to transient cerebral hypoperfusion. Beyond immediate symptoms such as dizziness and syncope, OH is associated with long-term risks including falls, fractures, cognitive decline, and cardiovascular morbidity. This review synthesizes current evidence on epidemiology, definitions, pathophysiology, diagnostic approaches, management strategies, and future directions. Four phenotypes, including initial, classical, delayed, and delayed recovery, represent a clinical continuum from transient to sustained autonomic failure. Diagnosis relies primarily on the active standing test, with tilt-table and beat-to-beat monitoring enhancing detection of atypical forms. Home and ambulatory blood pressure monitoring provide additional insight into supine hypertension and postprandial patterns. Management prioritizes symptom control and prevention of complications through stepwise strategies: Lifestyle modification, volume and salt expansion, compression therapy, and pharmacological agents such as midodrine, droxidopa, and fludrocortisone. Drug selection and dosing must account for comorbid hypertension and supine hypertension risk. Recent research highlights phenotype-specific prognostic differences and emerging options, including pyridostigmine, atomoxetine, and device-based abdominal compression. Digital phenotyping through home or beat-to-beat monitoring may enable personalized management. The evolving understanding of OH underscores the importance of individualized, evidence-based care aimed at functional improvement and reduction of adverse outcomes rather than strict normalization of blood pressure.

***Keywords:*** Orthostatic hypotension; Supine hypertension; Phenotyping; Tilt-table testing; Digital monitoring

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## 1. Introduction

Orthostatic hypotension (OH) is not merely limited to clinical definitions; it significantly reduces quality of life, leads to traumatic falls, shortens life expectancy, and increases the risk of various health problems, particularly cardiovascular diseases.[1] For these reasons,

the early recognition, comprehensive evaluation, and development of management strategies for OH are of great importance for both clinical practice and public health.

The prevalence of OH in the general population is approximately 5–10%. However, its incidence increases markedly with age; prevalence rises to 20–30% in individuals over 70 years of age, and may reach 40–50% in those aged 85 years and older. Among residents of long-term care facilities, the rates increase to 25–30%, while in those with neurodegenerative disorders such as Parkinson's disease or dementia; prevalence may reach even more striking levels.[2,3]

From a clinical perspective, OH is important not only because it produces symptoms but also due to its long-term effects. Prospective data show that OH increases morbidity due to falls and fractures, predisposes to cognitive decline, and is independently associated with cardiovascular mortality.[4-6]

The presence of hypertension increases the risk of developing OH. Underlying mechanisms include vascular stiffness, autonomic nervous system dysfunction, and the effects of antihypertensive medications.[7] Nevertheless, recent randomized controlled trials have shown that intensive blood pressure treatment does not absolutely increase the frequency of OH, but rather its cardiovascular benefits predominate. Therefore, asymptomatic OH alone does not justify the relaxation of antihypertensive treatment.[5,8]

### 1.1. Methodology of the review

This narrative review was conducted through a structured search of the PubMed, Scopus, and Google Scholar databases. The search included articles published between 2000 and 2025, using the following keywords and combinations: "orthostatic hypotension," "neurogenic orthostatic hypotension," "supine hypertension," "autonomic dysfunction," "tilt-table test," and "blood pressure variability." Additional references were identified from the bibliographies of relevant reviews and guidelines. Both clinical studies and major consensus statements were included to provide a comprehensive synthesis of definitions, mechanisms, diagnostic methods, and management strategies.

## 2. Definition and classification

OH is defined as a reduction of ≥20 mmHg in systolic blood pressure (SBP) or ≥10 mmHg in diastolic blood pressure (DBP) within 3 min of standing up from the supine or resting position, or on tilting to an angle of ≥60°. This criterion has long been accepted and is referenced in many current guidelines.[9,10]

However, OH is not restricted to this classical definition; it can be classified into several subtypes based on clinical and pathophysiological characteristics:

- Initial OH: Within the first 15 s of standing, a fall of ≥40 mmHg SBP or ≥20 mmHg DBP occurs, which rapidly recovers. This form is generally transient and characterized by short-lived symptoms, and has been defined particularly in studies using continuous (beat-to-beat) blood pressure recordings.[11] Recent expert consensus has suggested that the term "immediate orthostatic hypotension" may more accurately describe this phenomenon, as the blood pressure drop occurs within the first seconds of standing.[12] This terminology is gaining attention as an alternative to the traditional "initial" term used in earlier literature and guidelines.
- Classical OH: Occurring between 30 s and 3 min after standing, meeting the ≥20/10 mmHg criteria. This is the most common type encountered in clinical practice.[9]
- Delayed OH: Falls in blood pressure that occur beyond 3 min of standing, often considered to represent milder forms of autonomic failure.[9,11]
- Delayed blood pressure recovery: Blood pressure falls after standing but takes longer than 15 s to return to baseline; therefore, stabilization of the fall is delayed.[9]

In addition, OH can be categorized by etiology into two main groups:

- Neurogenic OH: Due to autonomic nervous system dysfunction. Disorders affecting the central or peripheral nervous system (*e.g.*, Parkinson's disease, multiple system atrophy (MSA), autonomic syndromes, diabetic neuropathy) fall into this group.[13]
- Non-neurogenic OH: Secondary to causes such as volume depletion (dehydration, blood loss), cardiac dysfunction, drug effects (diuretics, vasodilators, antihypertensives), or electrolyte disturbances.[9,13]

The definition and classification of OH are clinically relevant, as each subtype may differ in prognostic value, therapeutic approach, and management. The classical form is most commonly encountered, whereas initial and delayed forms are less frequent but may be overlooked, particularly in symptomatic patients. The main phenotypic categories and their diagnostic thresholds are summarized in Table 1.

## 3. Pathophysiology

OH occurs as a result of inadequate physiological responses to the sudden hemodynamic effects of gravity on standing. Under normal conditions, approximately 300–800 mL of blood pools in the legs and splanchnic region. This

reduces venous return and, consequently, stroke volume; if compensatory mechanisms are insufficient, a marked fall in systemic arterial pressure ensues.[14,15] The main compensatory mechanisms during postural change and the pathophysiologic disturbances responsible for OH are illustrated in Figure 1.

### 3.1. Normal compensatory mechanisms

In healthy individuals, several simultaneous mechanisms are activated in response to standing:

- Baroreflex response: Baroreceptors in the carotid sinus and aortic arch sense the drop in pressure and, through the medulla oblongata, increase sympathetic activity while reducing parasympathetic tone. As a result, heart rate rises, myocardial contractility increases, and arterial and venous vessels constrict.[2,16]
- Arterial and venous tone: Vasoconstriction of peripheral arterioles supports blood pressure by increasing peripheral resistance, while increased

**Table 1. Clinical phenotypes of orthostatic hypotension**

| Phenotype | Definition/criteria | Clinical relevance | References |
|---|---|---|---|
| Initial OH | ≥40 mmHg SBP or ≥20 mmHg DBP fall within first 15 s, rapid recovery | Often transient; beat-to-beat BP monitoring required | 11 |
| Classical OH | ≥20/10 mmHg fall within 3 min of standing | Most common form in practice | 9 |
| Delayed OH | BP fall occurs >3 min after standing | May represent early/mild autonomic dysfunction | 9,11 |
| Delayed BP Recovery | BP fall after standing, recovery >15 s | Suggests impaired compensatory kinetics | 9 |

Abbreviations: BP: Blood pressure; DBP: Diastolic blood pressure; OH: Orthostatic hypotension; SBP: Systolic blood pressure.

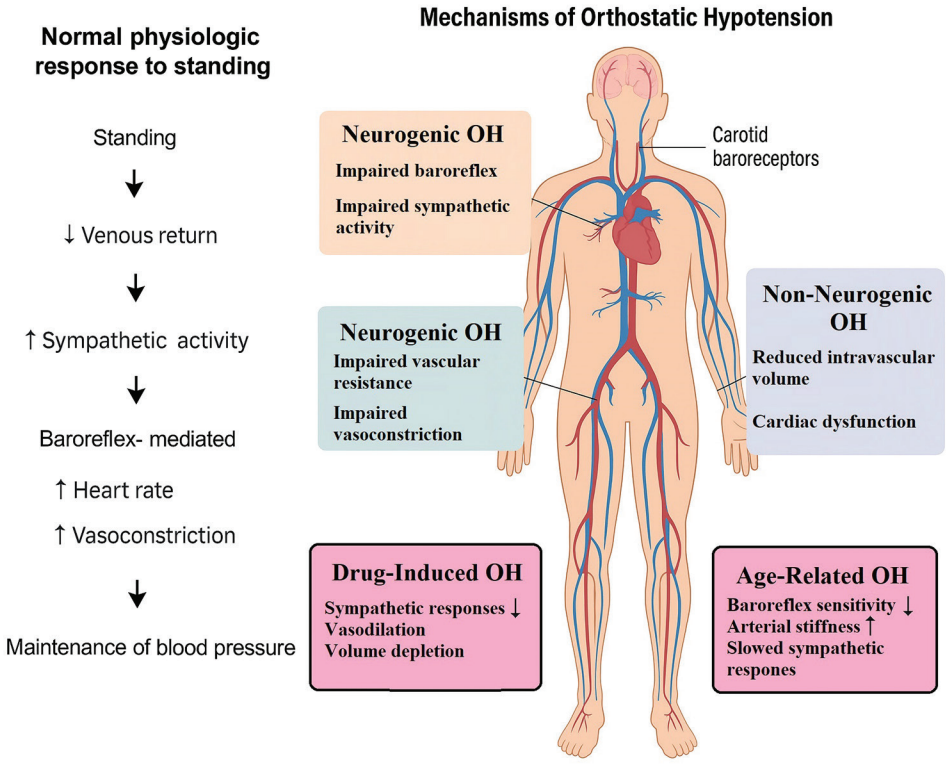


**Figure 1.** Overview of normal compensatory responses to standing and key pathophysiologic mechanisms, leading to orthostatic hypotension. The left panel illustrates the normal physiological response to standing, in which venous pooling triggers baroreceptor-mediated sympathetic activation, leading to increased heart rate and vasoconstriction that maintain blood pressure. Carotid baroreceptors play a central role in initiating compensatory reflexes. The right panel summarizes the principal mechanisms underlying orthostatic hypotension (OH). Neurogenic OH results from impaired baroreflex function or defective sympathetic vasoconstriction. Non-neurogenic OH arises from reduced intravascular volume or cardiac dysfunction. Drug-induced OH involves attenuation of sympathetic responses, vasodilation, or volume depletion, while age-related OH reflects decreased baroreflex sensitivity, arterial stiffness, and slowed sympathetic responses. Image created by the authors.

venous tone limits pooling. Splanchnic venous capacitance is particularly critical in this regard.[2]

- Hormonal regulation: With prolonged standing, the renin–angiotensin–aldosterone system is activated. Angiotensin II is a potent vasoconstrictor; aldosterone promotes sodium retention to support intravascular volume. Vasopressin (ADH), released from the posterior pituitary, further contributes by promoting water retention.[14]
- Muscle pump: Rhythmic contractions of the calf muscles propel venous blood upward through the deep veins, thereby supporting venous return. This mechanism is absent during prolonged immobility in the upright position, increasing the risk of OH.[14]

### 3.2. Pathophysiological disturbances

The development of OH reflects inadequacy or impairment of the above compensatory mechanisms:

- Neurogenic OH: Results from autonomic nervous system dysfunction. Parkinson's disease, MSA, pure autonomic failure, and diabetic neuropathy are among the most frequent causes. In this setting, norepinephrine release from sympathetic nerve terminals is reduced, leading to impaired vascular response and insufficient heart rate increase. Clinically, heart rate rises minimally (<10–15 bpm) on standing.[16,17]
- Non-neurogenic OH: Here, the nervous system is intact, but effective circulating volume is reduced. Conditions such as dehydration, blood loss, diuretic therapy, and advanced heart failure fall into this group; compensatory reflexes may remain intact, but the baseline reserve is inadequate.[7]
- Drug-induced OH: Antihypertensives (especially alpha-blockers, diuretics, nitrates), dopaminergic agents, and certain antidepressants may cause OH by suppressing sympathetic responses or inducing vasodilation.[7] Polypharmacy, especially in older adults, further amplifies this effect.
- Age-related changes: With advancing age, baroreflex sensitivity diminishes, arterial stiffness increases, and sympathetic responses are slowed. In addition, venous valve incompetence and a tendency toward venous pooling become more prominent. These changes explain the higher prevalence of OH in elderly populations.[2,18]
- Supine hypertension paradox: Patients with neurogenic OH often exhibit concomitant supine hypertension. The paradox of high blood pressure while supine but marked hypotension on standing complicates diagnosis and therapeutic strategies.[18]

### 3.3. Special situations

- Postprandial hypotension: Following meals, splanchnic vasodilation and increased blood flow predispose especially elderly and autonomic failure patients to OH.
- Post-exercise hypotension: Abrupt cessation of activity eliminates the muscle pump, thereby exacerbating venous pooling.
- Delayed OH: Slow-onset blood pressure falls occurring after more than 3 min of standing are often an early sign of autonomic dysfunction.[17]

## 4. Clinical findings

The clinical presentation of OH spans a wide spectrum. The most common manifestations are symptoms of orthostatic intolerance: Dizziness on standing, lightheadedness, unsteadiness, blurred or blackened vision, tinnitus, headache, difficulty concentrating, fatigue, and presyncope.[8,18,19] Symptoms typically develop within a few seconds to a few minutes and resolve rapidly on returning to the supine position.[2,18,19]

In more severe cases, syncope may occur, which is an important risk factor for falls and traumatic fractures, particularly in the elderly.[2,6] OH may also cause acute slowing of cognitive function and confusion; in the long term, recurrent episodes have been associated with dementia and cognitive decline.[6,20]

The severity and onset of symptoms are closely related to provoking factors. Morning hours, postprandial periods (postprandial hypotension), hot environments, abrupt cessation of exercise, alcohol intake, and prolonged motionless standing are the principal triggers that exacerbate OH symptoms.[2,18,21]

In addition to symptoms, certain clinical clues are diagnostically informative. The heart rate response provides insight into the underlying mechanism: in neurogenic OH, despite a drop in blood pressure, the increase in heart rate is minimal (<10–15 bpm), whereas in OH due to volume loss or medications, compensatory tachycardia is more prominent.[8,18,21] On physical examination in the orthostatic position, narrowing of pulse pressure, cool–pale extremities, and unsteady gait may be observed.

A particularly common finding in neurogenic OH is concomitant supine hypertension. In this situation, patients exhibit hypertensive values while supine but develop marked hypotension on standing; this paradox complicates both the symptom profile and therapeutic strategies.[10,19]

## 5. Diagnostic approach

If there is active clinical suspicion, the first step is the bedside active standing test: After at least 5 min of supine rest, the patient is brought to the standing position, and blood pressure and pulse are measured at the 1st and 3rd min. A fall of ≥20 mmHg SBP or ≥10 mmHg DBP constitutes the diagnostic criterion.[8,15,21]

If the bedside test is normal but clinical features persist, or if initial or delayed forms are suspected, beat-to-beat non-invasive blood pressure monitoring or tilt-table testing is recommended. Tilt testing is particularly used to provoke symptoms and findings and helps distinguish among different orthostatic forms.[8,21,22]

In individuals with hypertension, the diagnostic approach should be supplemented by home blood pressure monitoring or ambulatory blood pressure monitoring (ABPM), as orthostatic variability and patterns such as supine hypertension may only be captured at home or on ambulatory monitoring.[8,23]

The heart rate response is also an important clue during diagnostic evaluation: If the increase in heart rate accompanying the blood pressure fall is <10–15 beats/min, this favors neurogenic OH; larger increases suggest volume loss or non-neurogenic causes.[8,21,23]

In addition, the medication history (particularly diuretics, vasodilators, and antihypertensives) should be reviewed during clinical assessment; if drug effects contribute to orthostatic drops, dose adjustments may be required.[21,23]

Laboratory and basic tests may assist diagnosis: Complete blood count (anemia), electrolytes, renal function, glucose/HbA1c, and thyroid function.[21] If necessary, autonomic function testing (Valsalva maneuver, deep breathing test, quantitative sudomotor axon reflex test, heart rate variability tests) can further characterize autonomic dysfunction.[21,22] A summary of diagnostic modalities, including bedside, tilt, ambulatory, and autonomic function testing, is provided in Table 2.

## 6. Cardiovascular effects

OH is not merely a cause of symptomatic intolerance; in prospective studies, it has shown significant correlations with cardiovascular events, heart failure, coronary disease, and all-cause mortality.[5,10,24]

In community-based cohort studies, the presence of OH has been associated with increased mortality. For instance, in the meta-analysis by Angelousi *et al.*,[25] overall mortality was 36% higher among individuals with OH (HR ≈ 1.36). This finding suggests that OH may serve as a prognostic marker across diverse populations.

Regarding heart failure, some observational studies have reported a strong association between OH and the incidence of heart failure. Cross-sectional studies have identified OH as a risk factor predicting the development of heart.[26] Moreover, increased risks of coronary artery disease and arrhythmia in association with OH have been observed in various cohort analyses.[10,24]

However, conflicting findings also exist in the literature. For example, a meta-analysis confirmed the association of OH with cardiovascular events but suggested that in subgroups receiving intensive blood pressure lowering, OH did not increase risk.[5] Another study found no significant association between OH and cardiovascular events among individuals on intensive antihypertensive therapy.[24]

A recently published study presented separate analyses of cardiovascular events for initial (within the first 15 s) and sustained forms of OH in individuals aged ≥50 years. This study indicates that risk may differ according to the OH phenotype.[27]

In addition, links have been reported between OH and subclinical atherosclerosis: correlations have been found between the magnitude of postural blood pressure drop and carotid intima–media thickness and plaque burden.[28] This suggests that OH may reflect direct hemodynamic stress and endothelial dysfunction.

Taken together, the presence of OH, particularly when accompanied by advanced age, hypertension, and cardiovascular risk factors, has clinical importance

**Table 2. Diagnostic approach in orthostatic hypotension**

| Step/test | Methodology | Diagnostic value | References |
|---|---|---|---|
| Active standing test | BP and HR at first and third minute after standing | First-line, bedside, high specificity | 8,14,20 |
| Tilt-table test | Supine→60–70° tilt; continuous BP/HR monitoring | Differentiates initial/delayed forms | 8,20,21 |
| Home/ABPM | 24-h or home BP monitoring | Detects supine hypertension, postprandial OH | 8,22 |
| Autonomic function tests | Valsalva, HR variability, QSART | Confirms neurogenic OH | 20,21 |

Abbreviations: ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; HR: Heart rate; OH: Orthostatic hypotension; QSART: Quantitative sudomotor axon reflex test.

for long-term follow-up plans and risk stratification. Nevertheless, further prospective, controlled studies are needed to establish the independent prognostic effect of OH.

## 7. Treatment and management

The treatment of OH primarily aims to relieve symptoms, prevent falls, and enhance functional capacity rather than to normalize blood pressure values. Management begins with identification and correction of reversible factors. Drugs that may worsen OH, such as diuretics, vasodilators, alpha-blockers, and nitrates, should be reduced, discontinued, or substituted when possible. Patients should be assessed for hypovolemia and underlying conditions such as heart failure, adrenal insufficiency, or gastrointestinal fluid loss, and these should be corrected before specific therapy is initiated.[10,29] The stepwise therapeutic framework integrating lifestyle, pharmacologic, and special-case strategies is outlined in Table 3.

Lifestyle and non-pharmacological measures form the cornerstone of management and are recommended for all patients, either alone or in combination with medication. Adequate hydration (2–3 L/day) and liberal salt intake expand plasma volume, while rapid ingestion of 300–500 mL of water can acutely increase blood pressure through the osmopressor reflex. Behavioral strategies such as rising slowly, pausing before standing fully, avoiding hot environments and postprandial standing, and performing physical counter-maneuvers (leg crossing, calf and quadriceps contractions) help mitigate symptoms. Abdominal compression garments reduce venous pooling more effectively than lower-extremity stockings, and elevating the head of the bed by 10–20 cm minimizes nocturnal hypertension. Moderate physical activity and resistance training support venous return and improve orthostatic tolerance.[8,10,15,21]

Pharmacological therapy is reserved for patients with persistent symptoms despite optimal non-drug measures. Treatment must be individualized according to the OH type, comorbidities, and the presence of supine hypertension. Fludrocortisone enhances sodium retention and intravascular volume but carries risks of fluid overload and heart failure. Midodrine, a selective alpha-1 agonist, effectively increases vascular tone and is widely used, particularly in neurogenic OH. Droxidopa, a norepinephrine precursor, augments sympathetic tone and is beneficial in peripheral sympathetic failure. Pyridostigmine, an acetylcholinesterase inhibitor, and atomoxetine, a norepinephrine reuptake inhibitor, may be useful adjuncts, with pyridostigmine offering symptom control without exacerbating supine hypertension.[8,10,13,21,30-34] It should be noted that the availability of some pharmacologic agents discussed (*e.g.*, droxidopa, ampreloxetine) may vary between countries, and therapeutic choices should be adapted according to local drug accessibility and regulatory approval.

Therapeutic strategies should begin with low doses and gradual titration. The coexistence of supine hypertension necessitates short-acting agents and avoidance of late-day dosing. Combination therapy, such as midodrine plus fludrocortisone or adjunctive pyridostigmine, may enhance efficacy. Blood pressure should be monitored in both supine and upright positions, and side effects assessed regularly. In older adults or those with renal dysfunction, fluid and drug adjustments require particular caution.[21,30]

Special considerations include the management of patients with concomitant hypertension, in whom antihypertensive therapy should not be universally withdrawn but rather optimized through timing and agent selection. In inpatient or acute settings, careful fluid administration, gradual postural transitions, and supportive head-up positioning are essential. In neurogenic OH, treatment must balance symptomatic benefit with the risk of supine hypertension, guided by individualized assessment of autonomic dysfunction and medication burden.[10,21,29,30] The principal pharmacologic options, including their mechanisms of action, common starting doses, adverse effects, and levels of evidence, are summarized in Table 4.

## 8. Future directions

In recent years, research in OH has accelerated along two lines: (i) more refined phenotyping and prognostic

**Table 3. Management of orthostatic hypotension**

| Level | Interventions | Key points | References |
|---|---|---|---|
| Lifestyle & non-pharmacological | ↑ Fluid/salt, water bolus, slow rising, counter-maneuvers, compression stockings, head-up sleeping | First-line, universal | 8,10,20 |
| Pharmacological | Fludrocortisone, midodrine, droxidopa, pyridostigmine, atomoxetine | Individualized; consider supine HTN | 10,20,29-33 |
| Special cases | OH+hypertension; inpatient management; elderly/frail patients | Careful dose adjustment, avoid overtreatment | 20,28,29 |

Abbreviation: OH: Orthostatic hypotension.

**Table 4. Pharmacologic management of orthostatic hypotension**

| Agent | Mechanism of action | Common starting dose | Major side effects | Level of evidence | References |
|---|---|---|---|---|---|
| Midodrine | $\alpha_1$-adrenergic agonist→increases vascular tone | 2.5–10 mg orally, 2–3×/day | Supine hypertension, piloerection, scalp tingling | High | 8,10,20,29 |
| Fludrocortisone | Mineralocorticoid→sodium and water retention→expands plasma volume | 0.05–0.2 mg/day | Edema, hypokalemia, heart failure exacerbation | Moderate | 10,20,29 |
| Droxidopa | Synthetic NE precursor→augments sympathetic tone | 100–600 mg 3×/day | Headache, hypertension | High | 8,10,12,30 |
| Pyridostigmine | Acetylcholinesterase inhibition→enhances ganglionic transmission | 30–60 mg 2–3×/day | GI upset, muscle cramps | Moderate | 10,20,31,32 |
| Atomoxetine | NE reuptake inhibition→increases sympathetic outflow | 18–40 mg/day | Insomnia, tachycardia, anxiety | Low–moderate | 32,33 |

Abbreviations: GI: Gastrointestinal; NE: Norepinephrine.

modeling, and (ii) novel/improved pharmacological and device-based therapies. The line of evidence with direct impact on clinical practice has been a shift toward more precise characterization and more personalized therapeutic strategies through the systematic use of delayed/initial forms, heart rate response-based distinctions, and home/ambulatory monitoring.[8,15]

- Regarding prognostic updates: Throughout the 2020s, evidence has strengthened that classical and delayed OH are long-term risk markers: Major reviews and guidelines emphasize that delayed OH may represent an early/mild phenotype of autonomic dysfunction and may be associated with increased long-term mortality.[10,15] In addition, in an elderly cohort with coronary artery disease, OH was associated with a significant increase in cardiovascular mortality risk, supporting the notion that these phenotypes point not only to symptoms but also to hard outcomes.[35] Nonetheless, recent analyses indicating that OH does not necessarily increase event risk in the context of intensive antihypertensive therapy suggest that aggressive blood pressure control may be safe in appropriately selected patients.[5]
- New evidence and combinations in therapy: From 2023 to 2025, combination approaches have come to the fore: the combination of pyridostigmine + midodrine has shown additive benefit in orthostatic blood pressure reduction compared to monotherapies.[32] Comparative data between midodrine and droxidopa are accumulating; recent syntheses report that midodrine more robustly increases upright SBP but carries a higher risk of supine hypertension, whereas droxidopa appears more neutral in this regard.[31] On the other hand, safety signals regarding midodrine in heart failure with reduced ejection fraction (HfrEF, associations with more hospitalizations and mortality) have been published, necessitating more cautious use in patients with concomitant heart failure.[36]
- Norepinephrine transporter (NET) inhibitors and new molecules: In a recent double-blind, randomized crossover study, atomoxetine did not demonstrate superiority over placebo, limiting the translation of previous encouraging acute effects into routine practice.[33,34] By contrast, Phase 3 programs for ampreloxetine, a long-acting NET inhibitor, in neurogenic OH associated with MSA are ongoing; analyses reported between 2023 and 2025 indicate improvements in composite OH symptom scores, while final efficacy/safety conclusions await completion of ongoing trials.[37]
- Device-based/technological solutions: The hemodynamic efficacy of abdominal compression had been demonstrated in earlier randomized data; in 2024–2025, usability and safety-focused studies of inflatable abdominal binder designs were published. These platforms open a new area in terms of daily wearability and tailoring the effective pressure level to the patient.[38-40] In addition, home/ambulatory and beat-to-beat monitoring technologies facilitate routine detection of phenotypes such as initial OH and delayed recovery, accelerating the transition to the era of "digital phenotyping"; a 2024 American Heart Association statement supports the integration of these monitors into decision-making, particularly in hypertensive adults.[8]
- Personalization and targeted therapy in the near future: The forthcoming focus will be on developing "risk–benefit balanced" strategies that account for phenotype (neurogenic vs. non-neurogenic; initial/classical/delayed), coexisting supine hypertension, and comorbidities (especially HFrEF). Positioning NET inhibitors in selected subgroups (*e.g.*, MSA), testing device–drug combinations (*e.g.*, short-acting midodrine + personalized abdominal compression), and adequately powered prospective studies on long-term outcomes (falls, fractures, cardiovascular events, cognition) represent the greatest unmet needs in the field.[8,31,32,35-41]

Future research priorities should focus on addressing several unresolved questions regarding OH, particularly the delayed subtype. Delayed OH appears to represent an early or partial form of autonomic failure, yet its natural history, clinical trajectory, and potential reversibility remain poorly characterized. Longitudinal studies using continuous or ambulatory blood pressure monitoring could clarify whether delayed OH consistently progresses to classical OH and whether early lifestyle or pharmacological intervention can modify this course.[14]

Biomarker development is another unmet need. Although indices such as heart rate variability, plasma norepinephrine levels, and endothelial stress markers (*e.g.*, EASIX, inflammatory ratios) have shown promise, none have yet been validated for routine clinical use. Future work should aim to establish reproducible, phenotype-specific biomarkers to distinguish neurogenic from non-neurogenic forms and to predict symptom burden, cardiovascular risk, and treatment response. Integration of digital phenotyping and machine learning-based autonomic profiling could further improve predictive accuracy.[42]

Targeted management strategies should be explored in patient subgroups with particularly high unmet needs, such as those with co-existing supine hypertension, neurodegenerative disorders, or frailty. These populations are often excluded from clinical trials but face the greatest risk of adverse outcomes and therapeutic complications. Pragmatic, phenotype-driven studies assessing individualized dosing schedules, device-based compression technologies, and novel sympathomimetic or neuroprotective agents could help refine management algorithms.[10,15]

In summary, the future direction of OH research should move toward longitudinal characterization, biomarker-driven diagnosis, and precision-based therapy, with a focus on vulnerable subgroups and real-world applicability.

## 9. Conclusion

OH represents a systemic disorder rather than a simple postural fall in blood pressure. Its growing prevalence with aging and its impact on quality of life, morbidity, and cardiovascular outcomes highlight the need for structured screening and individualized management. Accurate diagnosis relies on standardized measurements, particularly the active standing test and, when necessary, tilt-table or beat-to-beat monitoring. Recognition of distinct phenotypes, including initial, classical, delayed, and delayed recovery, is essential, as each carries different prognostic and therapeutic implications.

Pathophysiologically, OH results from disturbances in autonomic, vascular, and hormonal mechanisms that maintain upright perfusion. The coexistence of supine hypertension, especially in neurogenic OH, remains a major therapeutic challenge. In practice, symptom-oriented treatment aimed at improving postural tolerance is prioritized over strict normalization of blood pressure. Non-pharmacological strategies, fluid and salt optimization, behavioral adjustments, compression therapy, and head-up sleeping form the foundation of care. Pharmacological options, including midodrine, droxidopa, and fludrocortisone, should be selected and titrated cautiously, considering comorbidities and the risk of supine hypertension. Adjunctive use of pyridostigmine or atomoxetine may provide additional benefit in selected patients.

Future management should advance toward phenotype-specific and personalized approaches that integrate home or ambulatory monitoring, wearable compression systems, and digital phenotyping. Standardized diagnostic criteria, long-term outcome studies, and pragmatic clinical trials targeting falls, fractures, cardiovascular events, and cognition are critical next steps. Early recognition and evidence-based, individualized therapy remain key to improving functional outcomes and reducing the overall burden of OH.

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The authors declare that they have no competing interests.

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## References


1. Palma JA, Kaufmann H. Epidemiology, diagnosis, and management of neurogenic orthostatic hypotension. *Mov Disord Clin Pract*. 2017;4(3):298-308.

   doi: 10.1002/mdc3.12478

2. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: Epidemiology, prognosis, and treatment. *J Am Coll Cardiol*. 2015;66(7):848-860.

   doi: 10.1016/j.jacc.2015.06.1084

3. Rose KM, Tyroler HA, Nardo CJ, *et al*. Orthostatic hypotension and the incidence of coronary heart disease: The atherosclerosis risk in communities study. *Am J Hypertens*. 2000;13(6 Pt 1):571-578.

   doi: 10.1016/s0895-7061(99)00257-5

4. Xin W, Mi S, Lin Z, Wang H, Wei W. Orthostatic hypotension and the risk of incidental cardiovascular diseases: A meta-analysis of prospective cohort studies. *Prev Med*. 2016;85:90-97.

   doi: 10.1016/j.ypmed.2016.01.007

5. Juraschek SP, Hu JR, Cluett JL, *et al*. Orthostatic hypotension, hypertension treatment, and cardiovascular disease: An individual participant meta-analysis. *JAMA*. 2023;330(15):1459-1471. doi: 10.1001/jama.2023.18497. Erratum in: *JAMA*. 2023;330(19):1915.

   doi: 10.1001/jama.2023.23332

6. Finucane C, O'Connell MD, Fan CW, *et al*. Age-related normative changes in phasic orthostatic blood pressure in a large population study: Findings from the irish longitudinal study on ageing (TILDA). *Circulation*. 2014;130(20):1780-1789.

   doi: 10.1161/CIRCULATIONAHA.114.009831

7. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: Diagnosis and treatment. *Am J Med*. 2007;120(10):841-847.

   doi: 10.1016/j.amjmed.2007.02.023

8. Juraschek SP, Cortez MM, Flack JM, *et al*. Orthostatic hypotension in adults with hypertension: A scientific statement from the American heart association. *Hypertension*. 2024;81(3):e16-e30.

   doi: 10.1161/HYP.0000000000000236

9. Freeman R, Wieling W, Axelrod FB, *et al*. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011;21(2):69-72.

   doi: 10.1007/s10286-011-0119-5

10. Fedorowski A, Ricci F, Hamrefors V, *et al*. Orthostatic hypotension: Management of a complex, but common, medical problem. *Circ Arrhythm Electrophysiol*. 2022;15(3):e010573.

    doi: 10.1161/CIRCEP.121.010573

11. Brignole M, Moya A, De Lange FJ, *et al*. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39(21):1883-1948.

    doi: 10.1093/eurheartj/ehy037

12. Benditt DG, Fedorowski A, Sutton R, *et al*. 'Transient immediate orthostatic hypotension' is preferable to 'initial' orthostatic hypotension. *Auton Neurosci*. 2025;260:103288.

    doi: 10.1016/j.autneu.2025.103288

13. Ju W, Sinn DI. Diagnosis and management of neurogenic orthostatic hypotension. *Ann Clin Neurophysiol*. 2023;25(2):66-77.

    doi: 10.14253/acn.2023.25.2.66

14. Gibbons CH, Freeman R. Clinical implications of delayed orthostatic hypotension: A 10-year follow-up study. *Neurology*. 2015;85(16):1362-1367.

    doi: 10.1212/WNL.0000000000002030

15. Wieling W, Kaufmann H, Claydon VE, *et al*. Diagnosis and treatment of orthostatic hypotension. *Lancet Neurol*. 2022;21(8):735-746.

    doi: 10.1016/S1474-4422(22)00169-7

16. Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: A pathophysiological approach. *Circulation*. 2009;119(1):139-146.

    doi: 10.1161/CIRCULATIONAHA.108.805887

17. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med*. 2008;358(6):615-624.

    doi: 10.1056/NEJMcp074189

18. Jordan J, Biaggioni I. Diagnosis and treatment of supine hypertension in autonomic failure patients with orthostatic hypotension. *J Clin Hypertens (Greenwich)*. 2002;4(2):139-145.

    doi: 10.1111/j.1524-6175.2001.00516.x

19. Dani M, Taraborrelli P, Panagopoulos D, *et al*. New horizons in the ageing autonomic nervous system: Orthostatic hypotension and supine hypertension. *Age Ageing*. 2022;51(8):afac150.

doi: 10.1093/ageing/afac150

20. Cremer A, Soumaré A, Berr C, *et al*. Orthostatic hypotension and risk of incident dementia: Results from a 12-year follow-up of the three-city study cohort. *Hypertension*. 2017;70(1):44-49.

    doi: 10.1161/HYPERTENSIONAHA.117.09048

21. Kim MJ, Farrell J. Orthostatic hypotension: A practical approach. *Am Fam Physician*. 2022;105(1):39-49. Erratum in: *Am Fam Physician*. 2022;106(4):365.

22. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(11):1294-1309.

    doi: 10.1016/j.jacc.2018.05.079

23. Jordan J, Biaggioni I. Raising awareness for cardiovascular autonomic dysfunction: The 2023 European society of hypertension guidelines revisited. *Clin Auton Res*. 2023;33(6):609-611.

    doi: 10.1007/s10286-023-00980-8

24. Juraschek SP, Taylor AA, Wright JT Jr, *et al*. Orthostatic hypotension, cardiovascular outcomes, and adverse events: Results from SPRINT. *Hypertension*. 2020;75(3):660-667.

    doi: 10.1161/HYPERTENSIONAHA.119.14309

25. Angelousi A, Girerd N, Benetos A, *et al*. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: A systematic review and meta-analysis. *J Hypertens*. 2014;32(8):1562-1571.

    doi: 10.1097/HJH.0000000000000235

26. Ricci F, Fedorowski A, Radico F, *et al*. Cardiovascular morbidity and mortality related to orthostatic hypotension: A meta-analysis of prospective observational studies. *Eur Heart J*. 2015;36(25):1609-1617.

    doi: 10.1093/eurheartj/ehv093

27. Geng H, Fang D, Chen X, Liu M. Cardiovascular outcomes in initial and sustained orthostatic hypotension: A retrospective cohort study. *J Clin Hypertens (Greenwich)*. 2025;27(2):e14976.

    doi: 10.1111/jch.14976

28. Juraschek SP, Daya N, Appel LJ, *et al*. Orthostatic hypotension and risk of clinical and subclinical cardiovascular disease in middle-aged adults. *J Am Heart Assoc*. 2018;7(10):e008884.

    doi: 10.1161/JAHA.118.008884

29. Peixoto AJ. Evaluation and management of orthostatic hypotension: Limited data, limitless opportunity. *Cleve Clin J Med*. 2022;89(1):36-45.

    doi: 10.3949/ccjm.89gr.22001

30. Kulkarni S, Jenkins D, Dhar A, Mir F. Treating lows: Management of orthostatic hypotension. *J Cardiovasc Pharmacol*. 2024;84(3):303-315.

    doi: 10.1097/FJC.0000000000001597

31. Grosu C, Noea O, Maştaleru A, Ignat EB, Leon MM. Neurogenic orthostatic hypotension in Parkinson disease-a narrative review of diagnosis and management. *J Clin Med*. 2025;14(2):630.

    doi: 10.3390/jcm14020630

32. Pavic NV, Zhang S, Maloof AG, *et al*. Pyridostigmine in the management of orthostatic hypotension: A systematic review and meta-analysis. *Open Heart*. 2025;12(1):e003106.

    doi: 10.1136/openhrt-2024-003106

33. Mwesigwa N, Millar Vernetti P, Kirabo A, *et al*. Atomoxetine on neurogenic orthostatic hypotension: A randomized, double-blind, placebo-controlled crossover trial. *Clin Auton Res*. 2024;34(6):561-569.

    doi: 10.1007/s10286-024-01051-2

34. Jung YJ, Kim A, Okamoto LE, Hong WH. Effects of atomoxetine for the treatment of neurogenic orthostatic hypotension in patients with alpha-synucleinopathies: A systematic review of randomized controlled trials and a focus-group discussion. *J Clin Neurol*. 2023;19(2):165-173.

    doi: 10.3988/jcn.2022.0018

35. Hu J, Chi J, Cai H, *et al*. Effect of orthostatic hypotension on long-term prognosis of elderly patients with stable coronary artery disease: A retrospective cohort study. *Front Cardiovasc Med*. 2024;11:1342379.

    doi: 10.3389/fcvm.2024.1342379

36. Wu MJ, Chen CH, Tsai SF. Safety of midodrine in patients with heart failure with reduced ejection fraction: A retrospective cohort study. *Front Pharmacol*. 2024;15:1367790.

    doi: 10.3389/fphar.2024.1367790

37. Freeman R, Kaufmann H, Biaggioni I, *et al*. *Precision Therapy with Ampreloxetine for Neurogenic Orthostatic Hypotension in Multiple System Atrophy*. [medRxiv Preprint]; 2025.

    doi: 10.1101/2025.08.12.25332833

38. Okamoto LE, Diedrich A, Baudenbacher FJ, *et al*. Efficacy of servo-controlled splanchnic venous compression in the treatment of orthostatic hypotension: A randomized comparison with midodrine. *Hypertension*. 2016;68(2):418-426.

    doi: 10.1161/HYPERTENSIONAHA.116.07199

39. Toma M, Jose R, Syed F, Devine T. A safety-centric study on the use of inflatable abdominal binders for managing orthostatic hypotension. *Clin Pract*. 2024;14(5):1737-1743.

    doi: 10.3390/clinpract14050138

40. Mitra K, Kunte S, Taube S, *et al*. Current landscape of compression products for treatment of postural orthostatic

tachycardia syndrome and neurogenic orthostatic hypotension. *J Clin Med*. 2024;13(23):7304.

doi: 10.3390/jcm13237304

41. Wolters FJ, Mattace-Raso FU, Koudstaal PJ, Hofman A, Ikram MA, Heart Brain Connection Collaborative Research Group. Orthostatic hypotension and the long-term risk of dementia: A population-based study. *PLoS Med*. 2016;13(10):e1002143.

doi: 10.1371/journal.pmed.1002143

42. Johansson M, Ricci F, Aung N, Sutton R, Melander O, Fedorowski A. Inflammatory biomarker profiling in classical orthostatic hypotension: Insights from the SYSTEMA cohort. *Int J Cardiol*. 2018;259:192-197.

doi: 10.1016/j.ijcard.2017.12.020