



Orthostatic Hypotension in Hypertensive Patients Hospitalized in Italian Internal Medicine Departments: FADOI-HYP-OP Study

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Abstract

Introduction Orthostatic hypotension (OH) is defined as a decline in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of at least 10 mmHg, within the first 3 min of standing.

Aim To evaluate the prevalence of OH and to identify the characteristics of patients with OH in hypertensive patients hospitalized in medical inpatient departments.

Methods A multicenter, observational, prospective study (FADOI-HYP-OP) included 1000 hypertensive inpatients from 29 Departments throughout Italy. Demographic, clinical data, blood pressure and the presence of comorbidities were recorded at baseline. Factors associated with OH were assessed in multiple logistic regression analysis.

Results The prevalence of OH was 25.1%. Factors independently associated with OH included disturbances of consciousness (RR 1.56, 95%CI 1.10–2.20; $p=0.01$), Parkinson's disease (RR 2.30, 95%CI 1.47–3.59; $p=0.0002$), type-1 diabetes

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(RR 1.72, 95%CI 1.05–2.80; $p=0.03$), respiratory comorbidities/diseases (RR 1.32, 95%CI 1.02–1.70; $p=0.04$), ischemic heart disease (IHD) (RR 1.20, 95%CI 1.01–1.43; $p=0.04$) and α 1-adrenergic receptor blockers use (RR 1.32, 95%CI 1.03–1.69; $p=0.03$).

Conclusions These real-world data indicate considerable prevalence of OH in hypertensive inpatients and confirm the association between OH and several common comorbidities as well as with use of α 1-adrenergic receptor blockers.

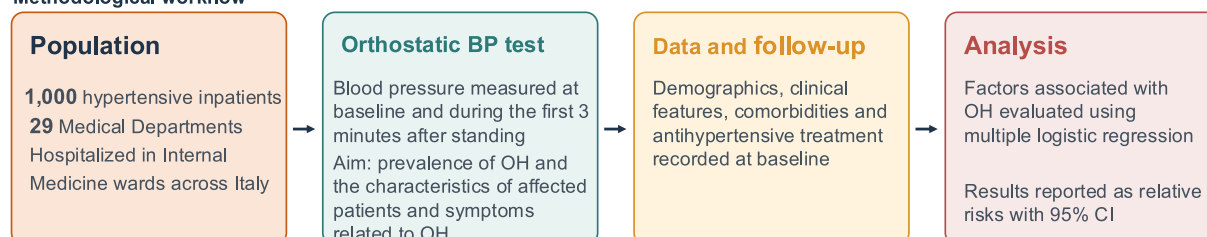
Clinical Trial registration: NCT05247060.

Graphical abstract

FADOI-HYP-OP: nationwide multicenter prospective observational study

Orthostatic hypotension in hospitalized hypertensive patients

Methodological workflow



Main findings

25.1%
prevalence of orthostatic
hypotension

Independent factors associated with OH

- Parkinson's disease **RR 2.30**
- Type 1 diabetes **RR 1.72**
- Disturbances of consciousness **RR 1.56**
- Respiratory comorbidities/diseases **RR 1.32**
- α 1-blockers use **RR 1.32**
- Ischemic heart disease **RR 1.20**

Clinical message

High prevalence of OH was associated with several comorbidities and with the use of certain antihypertensive medications in Internal Medicine clinical setting

Keywords Orthostatic hypotension · Hypertensive patients · Internal medicine · Real-world data

1 Introduction

Orthostatic hypotension (OH) is defined as a drop in blood pressure (BP) on standing [1, 2]. Although a definite agreement has never been achieved, it is generally accepted that the diagnosis of OH is based on a decline in systolic BP of at least 20 mmHg or in diastolic BP of at least 10 mmHg within 3 min of standing, starting from at least 5 min in either the sitting or the supine position [1–3]. Measurement of standing BP levels, regardless of the presence of hypertension, is not routinely recommended in clinical practice. However, it is encouraged in older, treated hypertensive, diabetic patients and, in general, in people having specific factors potentially favoring a significant orthostatic BP decrement [3].

OH increases the risk of falls [4], cardiovascular disease [5], depression [6], cognitive decline [7], hospitalizations or emergency department visits [8] and death [9]. It is usually caused by failure of the autonomic reflex, volume depletion, and/or adverse reaction to antihypertensive and/or other

medications [9, 10]. In specific conditions, particularly represented by the Parkinson's disease, the dangerous mixture of autonomic failure and medications can result in OH with supine hypertension [11, 12]. Symptoms on presentation of OH are commonly related to cerebral hypoperfusion. However, the drop in BP is commonly asymptomatic, thus leading to an even more marked increment in its negative consequences [13].

As expected, OH and hypertension often coexist, particularly in elderly hypertensives with multiple comorbidities and/or taking numerous medications [1, 2, 14]. The management of this coexistence is challenging, since antihypertensive treatment should be reduced in order to counteract hypotension while maintaining an adequate hypertension control [1, 2]. In this context, OH has been widely investigated in hospitalized Internal Medicine patients [15], with inconclusive results and a prevalence ranging from 22 [16] to 75% [17]. Limited information is available in this regard in Italian patients [18, 19].

Aim of the Orthostatic hypotension in hypertensive patients hospitalized in Italian Internal Medicine

Departments (HYP-OP) Study was: (1) to investigate the prevalence of OH in hypertensive patients who were hospitalized because of any reason and were not aware of this condition; (2) to describe the characteristics of affected patients and symptoms related to OH.

2 Methods

2.1 Study Design and Setting

HYP-OP was a prospective observational multicenter national study, promoted, sponsored and coordinated by the FADOI Foundation (the Italian Scientific Society of Hospital Internal Medicine) which provided the scientific and operational coordination, in collaboration with the Italian Society of Hypertension (SIIA). Details on the protocol are reported in the paper describing the rationale and design [20].

Investigators enrolled consecutive adult hypertensive patients hospitalized in the Internal Medicine Departments with hypertension either previously known or discovered on admission. Patients were enrolled in 29 Italian Internal Medicine Departments (from October 2018 to Novembre 2022), reasonably representative of this setting on a nationwide basis, by considering geographical distribution, characteristics of the hospital.

The study was divided in two phases:

- (1) In the cross-sectional phase 1, the hospitalization, clinical data were collected from consecutive patients with arterial hypertension admitted to Internal Medicine and able to assume the upright position;
- (2) in phase 2, the follow-up (FU), health status of participants was recorded, after 6–12–24–36 months from the index hospitalization, by telephone contact or clinical visit, if already scheduled, reporting falls, cardiovascular events (stroke, TIA, acute myocardial infarction, arrhythmias) or death. The results of phase 2 will be discussed in a separate publication.

2.2 Ethical Clearance

The study, following the approval of the protocol (FADOI-HYP-OP protocol code FADOI.02-2018) by local Ethics Committees, was carried out in full compliance with the Declaration of Helsinki and the principles of Good Clinical Practice; signed informed consent was collected from each patient. ClinicalTrials.gov registration number: NCT05247060.

2.3 Study Population

The cohort consisted of 1000 patients with hypertension either previously known or discovered on admission. The diagnosis of hypertension was made in accordance with the 2018 European Society of Hypertension (ESH) guidelines for a systolic BP (SBP) at least 140 mmHg or diastolic BP (DBP) at least 90 mmHg on repeated measurements, or independently of BP values for people taking anti-hypertensive medications.

2.4 Blood Pressure Measurement

Participants underwent three measurements of BP and heart rate, one after 3 min in a sitting position and two in a standing position (after 1 min and after 3 min), using locally available, validated semi-automatic BP devices equipped with cuffs of appropriate size based on arms circumference.

For the analysis the diagnosis of OH was based on a decline in SBP of at least 20 mmHg or in DBP of at least 10 mmHg within 3 min of standing, starting from at least 5 min in either the sitting or the supine position.

2.5 Data Collection

Demographic and clinical characteristics were recorded for each patient, as well as laboratory variables and drug therapies at the time of admission and during the hospital stay. Data were recorded in study-specific electronic case report form, based on contents of the hospital charts. All 1000 adult consecutive hypertensive patients with signed informed consent were enrolled, excluding only patients unable to stand up for a few minutes. Recorded variables included BP and heart rate in a sitting position, and subsequently, after 1 and 3 min from the assumption of the standing position. Other clinical and anamnestic parameters included: Charlson Index, lifestyle habits, cognitive status (Mini Mental Status Examination; MMSE), history of falls, pharmacological treatments, with particular focus on the antihypertensive therapy, Frailty Index (Short Physical Performance Battery; SPPB). Additionally, disturbances of consciousness (DOC) and difficulty in maintaining an upright position and the evaluation of visual disturbances were registered; they were considered if clinically manifesting with dizziness, blurred vision, unsteadiness, pre-syncope, and syncope, often associated with a failure of compensatory tachycardia.

Other parameters/events recorded were drug-related adverse reactions and in-hospital death.

Lastly, after 6–12–24–36 months from the hospitalization, falls and cardiovascular events (i.e. stroke, TIA, myocardial infarction, arrhythmias) or death were recorded.

Table 1 Demographic and clinical characteristics of the general population of patients with or without orthostatic hypotension at hospitalisation admission

	General population N = 1000 (100%)	Orthostatic hypotension		p-value
		Yes 251 (25.1%)	No 749 (74.9%)	
<i>Demographic characteristics</i>				
Age ≥ 75 years	523 (52.3%)	145 (57.8%)	378 (50.5%)	0.05
Male sex	597 (59.7%)	159 (63.4%)	438 (58.5%)	0.18
<i>In-hospital sitting blood pressure and heart rate</i>				
Systolic Blood Pressure (mm/Hg) mean (± SD)	130.5 (±19.4)	135 (± 22.3)	137 (± 22.0)	0.26
Diastolic Blood Pressure (mm/Hg) mean (± SD)	74.6 (±11.3)	77 (±12.0)	76.2 (±11.7)	0.75
Heart rate (bpm) mean (± SD)	77.7 (±14.4)	79.4 (±15.8)	79.5(±15.5)	0.95
Systolic Blood Pressure < 120 mm/Hg	163 (16.3%)	50 (19.9%)	113 (15.1%)	0.06
Systolic/diastolic Blood Pressure < 120/70 mm/Hg	77 (7.7%)	24 (9.6%)	53 (7.1%)	0.18
<i>Symptoms</i>				
Visual disturbances	149 (14.9%)	40 (16.0%)	109 (14.6%)	0.59
Disturbances of consciousness	35 (3.5%)	15 (6.0%)	20 (2.7%)	0.006
Difficulty in maintaining an upright position	86 (8.6%)	30 (12.0%)	56 (7.5%)	0.02
Dizziness	151 (15.1%)	48 (19.1%)	103 (13.8%)	0.03
Other	37 (3.7%)	11 (4.4%)	26 (3.5%)	0.50
<i>Cardiovascular comorbidities</i>				
Peripheral arterial disease	94 (9.4%)	32 (17.7%)	62 (8.3%)	0.03
Ischemic heart disease	296 (29.6%)	93 (37%)	203 (27.1%)	0.002
Stroke	55 (5.5%)	16 (6.4%)	39 (5.2%)	0.47
TIA	49 (4.9%)	11 (4.4%)	38 (5.1%)	0.67
Heart failure	213 (21.3%)	48 (9.1%)	165 (22%)	0.34
Others cardiovascular comorbidity	430 (43%)	119 (47.4%)	311 (41.5%)	0.10
<i>Neuropsychiatric comorbidities</i>				
Major depression	26 (2.6%)	6 (2.4%)	20 (2.7%)	0.81
Alzheimer's disease	3 (0.3%)	0 (0%)	3 (0.4%)	ns
Parkinson's disease	10 (1%)	7 (2.8%)	3 (0.4%)	<0.0001
Others neuropsychiatric comorbidity	92 (9.2%)	28 (11.2%)	64 (8.5%)	0.20
<i>Metabolic comorbidities</i>				
Type 1 diabetes	15 (1.5%)	7 (2.8%)	8 (1.1%)	0.02
Type 2 diabetes	306 (30.6%)	69 (27.5%)	237 (21.6%)	0.22
Diabetes (type 1 or type 2)	318 (31.8%)	76 (30.3%)	242 (32.3%)	0.55
Hypothyroidism	112 (11.2%)	24 (9.6%)	88 (11.7%)	0.35
Hyperthyroidism	16 (1.6%)	5 (2.0%)	11 (1.5%)	0.55
Others metabolic comorbidity	153 (15.3%)	37 (50%)	116 (43%)	0.28
<i>Respiratory comorbidities/diseases</i>				
Asthma	22 (2.2%)	7 (2.8%)	15(2.0%)	0.44
COPD	230 (23.0%)	64 (25.5%)	166 (22.2%)	0.27
Others respiratory comorbidities/diseases	87 (8.7%)	29 (11.5%)	58 (7.7%)	0.05
<i>Gastro-pancreatic comorbidities</i>				
Cirrhosis of the liver	20 (2%)	4 (1.6%)	16 (2.1%)	0.61
Chronic inflammatory disease	14 (1.4%)	5 (2.0%)	9 (1.2%)	0.32
Peptic ulcer	34 (3.4%)	11 (4.4%)	23 (3.1%)	0.30
Other gastro-pancreatic comorbidity	213 (21.3%)	48 (19.1%)	165 (22.0%)	0.34
<i>Osteoarticular comorbidities</i>				
Rheumatoid arthritis	9 (0.9%)	3(1.2%)	6 (0.8%)	0.54
Osteoporosis	78 (7.8%)	14 (5.6%)	64 (8.5%)	0.15
Others osteoarticular comorbidity	138 (13.8%)	31 (12.3%)	107 (14.3%)	0.45
<i>Oncological comorbidities</i>				
Local	151 (15.1%)	34 (13.5%)	117 (15.6%)	0.43
Metastatic	28 (2.8%)	8 (3.2%)	20 (2.7%)	0.66

Table 1 (continued)

	General population N=1000 (100%)	Orthostatic hypotension		<i>p</i> -value
		Yes 251 (25.1%)	No 749 (74.9%)	
Other comorbidities	438 (43.8%)	110 (43.8%)	328 (43.8%)	0.99
<i>Chronic kidney disease</i>				
Mild	295 (29.5%)	65 (27.5%)	230 (32.8%)	0.11
Moderate IIIa	186 (18.6%)	43 (18.2%)	143 (20.4%)	
Moderata IIIb	178 (17.8%)	57 (24.1%)	121 (17.2%)	
Serious	91 (9.1%)	25 (10.6%)	66 (9.4%)	0.09
Anemia	526 (52.6%)	144 (60.3%)	382 (53.9%)	
<i>Drugs for hypertension</i>				
No drugs	39 (3.9%)	14 (5.6%)	25 (3.3%)	0.85
Diuretics	497 (49.7%)	126 (50.2%)	371 (49.5%)	
Beta-blockers	475 (47.5%)	115 (45.8%)	360 (48.1%)	
Calcium channel blockers	381 (38.1%)	99 (39.4%)	282 (37.6%)	0.61
ACE-inhibitors	401 (40.1%)	97 (38.6%)	304 (40.6%)	0.59
AT1 antagonists	284 (28.4%)	59 (23.5%)	225 (30.0%)	0.05
Alpha1 antagonists	83 (8.3%)	31 (12.3%)	52 (6.9%)	0.004
At central level	13 (1.3%)	4 (1.6%)	9 (1.2%)	0.62
<i>Charlson index</i>				
Charlson index mean ($\pm$ SD)	2.5 ($\pm$ 2.1)	2.6 ($\pm$ 2.0)	2.4 ($\pm$ 2.1)	0.08
Min-Max	0–11	0–10	0–11	
Charlson Index=0	170 (17.0 %)	33 (13.2%)	137 (18.3%)	
Charlson Index=1	209 (20.9%)	57 (22.7%)	152(20.3%)	0.24
Charlson Index=2	208 (20.8%)	51 (20.3%)	157 (21.0%)	0.06
Charlson Index=3	147 (14.7%)	42 (16.7%)	105 (14.0%)	0.67
Charlson Index=4	102 (10.2%)	22 (8.8%)	80 (10.7%)	0.62
Charlson Index=5	72 (7.2%)	16 (6.4%)	56 (7.5%)	0.07
Charlson Index $\leq$ 5	908 (90.8%)	221(88.1%)	687 (91.7%)	0.02
Charlson Index > 5	92 (9.2%)	30	62	

SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; ACE, angiotensin converting enzyme; AT1: Angiotensin II Type 1 receptor

2.6 Sample Size Definition and Statistical Analysis

A sample size of 1000 patients was considered adequate to document a reliable estimate of a hypothetical prevalence of OH in the studied cohort of $12 \pm 3\%$ (statistical power of 80%, alpha error: 5%). Descriptive statistics were performed by calculating mean and standard deviation (SD) or median for continuous variables and absolute and relative frequencies for categorical variables. Prevalence of OH was reported with the corresponding 95% confidence interval (CI) corrected for continuity. Multivariate analysis model was carried out to evaluate the possible association between the presence of OH (primary end-point) and covariates selected on the basis of their clinical plausibility. Variables were selected if the relative *p*-value in univariate analysis was ≤ 0.1 . Multivariate adjusted relative risk (RR) for OH was calculated adjusting for confounders in logistic regression models. *P*-value < 0.05 was considered as statistically significant. All analyses were performed using SAS version 9.4).

3 Results

3.1 Characteristics of the Study Population

A total of 1000 patients were enrolled; the study population characteristics are presented in Table 1. Patients were elderly, the mean age was 72.5 ± 11.9 years, and 52.3% were ≥ 75 years old. The prevalence of comorbidities was very high with 16.4% of patients with Charlson Index ≥ 5 and about 60% of the population having 3 or more comorbidities mainly represented by cardiovascular (CV) diseases, anemia, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes. Nearly 63% of patients had the SPPB less than 9 indicating a moderate impairment of physical performance. Approximately one out of 4 patients had below-normal cognitive functions with a MMSE Score ≤ 24 (Table 2).

Table 2 Frailty assessed with short physical performance battery (SPPB) and level of cognitive decline assessed with Mini Mental State Examination (MMSE) both at baseline and association with orthostatic hypotension

	General population N= 1000 (100%)	Orthostatic hypotension		Chi- Square <i>P</i> value
		Yes	No	
<i>Short physical performance battery (SPPB) score</i>				
SPPB Score ≤ 2	62 (6.2%)	19 (7.6%)	43 (5.7%)	0.55
SPPB Score 3–9	565 (56.5%)	142 (56.6%)	423 (56.5%)	
SPPB Score ≥ 10	373 (37.3%)	90 (35.9%)	283 (37.8%)	
<i>Mini-mental state examination (MMSE) score</i>				
MMSE Score ≤ 18	37 (3.7%)	13 (5.2%)	24 (3.2%)	0.14
MMSE Score 19–24	230 (23.0%)	49 (21.3%)	181 (24.2%)	
MMSE Score ≥ 25	733 (73.3%)	189 (75.3%)	544 (72.6%)	

3.2 Patients with Orthostatic Hypotension

Of the 1000 patients enrolled, 251 (25.1%, 95% CI 22.5–27.9) were OH patients; of these 82 patients (8.2%) have a decline at least 20 mmHg in SBP, 98 (9.8%) patients have a decline at least 10 mmHg in DBP and 71 patients (7.1%) have both by decline SBP and DBP.

3.3 Factors Associated with Orthostatic Hypotension

Univariate e multivariable analyses (Table 3) demonstrated that several factors were associated with OH; in the univariate analyses, factors were age ≥ 75 years, disturbances of consciousness, other respiratory comorbidities/diseases, Parkinson's disease, peripheral arterial disease, ischemic heart disease, type-1 diabetes, and alpha-1 antagonist use, whereas AT1 antagonist therapy showed a borderline inverse association. In the multivariable logistic regression

model, the strongest predictor of OH was Parkinson's disease (RR 2.30, 95% CI 1.47–3.59; $p=0.0002$), followed by disturbances of consciousness (RR 1.56, 95% CI 1.10–2.20; $p=0.01$), type-1 diabetes (RR 1.72, 95% CI 1.05–2.80; $p=0.03$), alpha-1 antagonist use (RR 1.32, 95% CI 1.03–1.69; $p=0.03$), other respiratory comorbidities/diseases (RR 1.32, 95% CI 1.02–1.70; $p=0.04$), ischemic heart disease (RR 1.20, 95% CI 1.01–1.43; $p=0.04$), and AT1 antagonist therapy ($p=0.13$). Age ≥ 75 years ($p=0.18$), peripheral arterial disease ($p=0.21$), did not show significant association after adjustment.

4 Discussion

Prevalence of OH varies widely across studies and ranges from $<5\%$ to more than 50%, depending on methodological and demographic factors, population characteristics, BP measurement technique and clinical context [21, 22]. Higher OH rates are observed in institutional/hospital settings than in community samples and commonly the prevalence is about 30% or more in geriatric inpatient cohorts [23, 24].

In our study, we aimed to define the prevalence and the clinical phenotype of patients with OH in patients admitted in Internal Medicine Department and to determine whether OH is associated with higher total and cardiovascular events or higher cardiovascular risk in a large, representative group of elderly inpatients of both sexes.

In our cohort, having an average age of 72.5 years, prevalence of OH was 25%. This finding can be compared with two other Italian studies. The study by Alli et al. reported a considerably lower prevalence (13.8%) [18], most likely because it included outpatients randomly recruited in general practices while our study included inpatients of internal medicine departments. On the other hand, a similar prevalence of persistent OH (27.1%) as in our cohort was reported by Pasina et al. [19], in a much smaller ($N=85$) cohort of Internal Medicine inpatients. This latter study reported additionally a considerable proportion of patients

Table 3 Factors associated with orthostatic hypotension in univariate and multivariable logistic regression analysis

	Univariate logistic regression analysis			Multivariable logistic regression analysis		
	RR	(95% CI)	p	RR	(95% CI)	p
Age ≥ 75 years	1.25	1.00–1.55	0.05	1.12	0.95–1.32	0.18
Disturbances of consciousness	1.75	1.18–2.61	0.006	1.56	1.10–2.20	0.01
Others respiratory comorbidities/diseases	1.37	1.00–1.88	0.05	1.32	1.02–1.70	0.04
Parkinson's disease	2.84	1.86–4.32	<0.0001	2.30	1.47–3.59	0.0002
Peripheral arterial disease	1.41	1.04–1.91	0.03	1.17	0.91–1.51	0.21
Ischemic heart disease	1.40	1.13–1.74	0.002	1.20	1.01–1.43	0.04
Type 1 diabetes	1.88	1.08–3.27	0.02	1.72	1.05–2.80	0.03
AT1 antagonists	0.77	0.60–1.00	0.05	0.86	0.71–1.04	0.13
Alpha1 antagonists	1.56	1.15–2.10	0.004	1.32	1.03–1.69	0.03

with occasional OH (48.2%). It should be noted that the participants in the study of Pasina et al. were considerably older (mean age 79.6 years) than in our study.

Our study identified several factors independently associated with OH.

Parkinson's disease—OH is a common non-motor symptom of Parkinson's disease (PD) and results from autonomic nervous system dysfunction and sympathetic denervation [1]. In PD, degeneration of sympathetic nerves and accumulation of α -synuclein impair the release of norepinephrine leading to a failure of the autonomic nervous system to adequately regulate BP during postural change [25]. Moreover, dopaminergic medications used to treat PD - such as levodopa and dopamine agonist - can further worsen OH [1, 25, 26].

In our study PD was associated with more than doubled risk of developing OH; this finding confirms the need to actively assess PD patients for impaired BP regulation and OH in order to improve patient safety and quality of life.

Diabetes mellitus. OH is widely recognized as a frequent and clinically relevant complication of DM, especially in patients with long-standing disease and poor glycemic control [27]. The primary link between DM and OH is diabetic autonomic neuropathy but other diabetes-related factors may also contribute to OH, including osmotic diuresis, volume depletion, endothelial dysfunction, arterial stiffness, and impaired activation of the renin-angiotensin-aldosterone system. [28, 29].

In our cohort type 1 DM was a potent independent predictor of OH, associated with over 70% higher OH risk than in non-diabetic patients. Interestingly, this relationship was not evident for the more common type 2 DM. This in apparent contrast with population data showing that symptoms of autonomic neuropathy are more common in type 2 DM and the prevalence of orthostatic intolerance is similar [30]. However, the impact of DM on autonomic function largely depends on its duration and on long-term metabolic control, which were not necessarily comparable between our sample and general population data.

Disorders of consciousness (DOC) typically result from central nervous system abnormalities, such as disruption of signaling in the ascending reticular activating system, thalamo-cortical circuits or widespread cortical networks responsible for wakefulness and awareness. They may involve global neurological symptoms which reflect diffuse cortical or subcortical dysfunction and focal neurological symptoms which often depend on abnormal cranial nerve function [31, 32]. The presence of these abnormalities configures a particular form of OH, namely neurogenic orthostatic hypotension, often associated with a failure of compensatory tachycardia, a hallmark of the neurogenic form [1, 3, 21, 33].

In our study patients with DOC had a OH risk increased by 56%; an early identification of DOC-OH association is thus essential to reduce falls, syncope, and impaired functional independence.

Alpha-adrenergic receptor antagonists (α -blockers) widely used in the management of hypertension and lower urinary tract symptoms and disease (i.e. prostatic hyperplasia) highly prevalent conditions in older patients. Their mechanism of action inherently (arterial and venous vasodilation caused by α 1-receptor blockade) predisposes patients to disturbances in orthostatic BP regulation. [21, 33, 34]. In particular, non-selective agents, such as phenoxybenzamine and phentolamine, and non-uroselective α 1-blockers, including prazosin, doxazosin, and terazosin, exert more pronounced systemic vasodilatory effects and are therefore more frequently associated with symptomatic OH. In contrast, uro-selective α -blockers (eg. tamsulosin) exert minimal influence on systemic vascular tone, resulting in a comparatively lower incidence of OH [3, 35, 36].

In our cohort, patients taking α 1-blockers had a risk of having OH increased by more than 32% and for these patients the implementation of mitigation strategies, such as gradual dose titration, nighttime initiation of therapy and patient selection, can significantly reduce the risk and severity of orthostatic events.

Respiratory disease Chronic obstructive pulmonary disease (COPD) was among most frequent comorbidities in our sample but it was not associated with incidence of OH.

Other respiratory diseases such as interstitial lung disease, pulmonary fibrosis and sleep disordered breathing may contribute to OH due to severe hypoxemia, autonomic dysfunction and chronic right heart strain especially in case of advanced, long-standing disease [37, 38]. Neurodegenerative respiratory syndromes diseases like multiple system atrophy (MSA) or Parkinson's disease may also favour OH via autonomic dysfunction and respiratory involvement [39]. In our study, the presence of others comorbidities/respiratory diseases (with asthma and COPD excluded), increased the risk of OH by 32%, however, our data do not allow to identify any specific respiratory condition underlying this difference.

Coronary artery disease—OH is frequently observed in older adults and in patients with CV comorbidities and as in our patients coronary artery disease (CAD) was associated with the risk of OH increased by 20%.

From a pathophysiological perspective, CAD may be linked with OH through several common mechanisms, including increased arterial stiffness, endothelial dysfunction and impaired baroreceptor-mediated autonomic regulation of BP [21, 34]. Also, pharmacologic treatments commonly used in patients with CAD, including nitrates, beta-blockers, diuretics, and ACE inhibitors, may exacerbate OH by

inducing vasodilation, volume depletion, or blunting of reflex tachycardia [35, 40]. This association may have clinical consequences as acute hypotensive episodes may reduce coronary perfusion, precipitating ischemic events [21, 41]. Our data reinforce the need for an integrated approach to patients with OH and CAD, balancing the reduction of long-term ischemic risk with the prevention of hypotensive complications. In this respect, strategies include careful titration of antihypertensive and antianginal medications and non-pharmacologic measures such as gradual positional changes and close monitoring of orthostatic BP responses.

Overall, our data emphasize that OH should not be simply considered as a BP drop but rather as a distinct clinical phenotype highly prevalent in Internal Medicine inpatient population, both in normotensives and hypertensives. It reflects impaired autonomic regulation, vascular stiffness, hypovolemia and/or medication effects. This phenotype includes symptoms, signs, autonomic features, hemodynamic patterns and is commonly associated with comorbidities such as DM, PD and respiratory diseases [33, 34].

5 Conclusions

This prospective, nationwide study aimed to assess the phenotype of patients with orthostatic hypotension (OH) among hypertensive individuals hospitalized in Internal Medicine Departments. It provides real-world data from a large patient sample representative of the Italian setting. The prevalence of OH was relatively high and was associated with several comorbidities and with the use of certain antihypertensive medications.

Our results suggest several possible areas where current clinical practice may improve. First, the screening for OH should be mandatory among internal medicine inpatients. A well-standardized orthostatic BP measurement represents a simple way to identify this common condition thus allowing to mitigate the associated risks and to trigger an active search for underlying conditions, in particular for autonomic dysfunction. A careful review of chronic treatments is mandatory in OH patients with a particular attention to alpha-1-agonists, which, while representing in current guidelines a medication class basically reserved for resistant hypertensive patients, are still commonly used in older and frail patients at high risk of OH.

Further research is warranted to confirm these findings in different clinical settings and populations and to explore optimal management strategies.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval and Consent to Participate The study, conducted according to the guidelines of the Declaration of Helsinki, was approved by the Ethics Committee of the study's coordinating center (Comitato Etico per le Province di L'Aquila e Teramo), and then by the local Ethics Committee of each and every participating center (Protocol code FADOI.02-2018 FADOI-Hyp-Op Study; date of approval 07/06/2018). All investigations were conducted according to the principles set out in the Declaration of Helsinki. Once the study had been authorized by the Ethics Committees of all participating centers, written informed consent was requested from all enrolled patients.

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