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Orthostatic hypotension in hospitalized hypertensive patients admitted to internal medicine wards: rationale and design of the HYP-OP Study

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Abstract
Orthostatic hypotension (OH) is common yet frequently underrecognized in older adults and in patients with arterial hypertension (AH). OH is associated with falls, cardiovascular (CV) events, cognitive decline, and mortality. Despite guideline recommendations, orthostatic blood pressure (BP) measurement is not systematically performed in internal medicine wards.
The objective of the study protocol is to estimate the prevalence of OH in hypertensive patients hospitalized in internal medicine units, to identify clinical factors independently associated with OH, and to evaluate the prognostic impact of OH on long-term outcomes.
The HYP-OP Study is a national, multicenter, prospective, observational cohort study conducted in approximately 30 internal medicine units in Italy. Overall, 1000 consecutive adult patients with known hypertension or newly diagnosed AH during hospitalization were enrolled. BP and heart rate were measured after at least 5 minutes of rest in the seated position and again after standing for 1 and 3 minutes according to a standardized protocol. During the hospitalization, demographic, clinical, laboratory, cognitive (Mini-Mental State Examination), frailty/physical performance (Short Physical Performance Battery), comorbidity burden (Charlson Comorbidity Index), and pharmacological data were collected. Follow-up was scheduled at 6, 12, 24, and 36 months after discharge to assess falls, major CV events (stroke, transient ischemic attack, myocardial infarction, arrhythmias), and all-cause mortality.
The primary endpoint is the prevalence of OH and the identification, through multivariate analysis, of clinical factors independently associated with OH. Secondary analyses will assess the prognostic value of OH for subsequent falls, major CV events, and mortality.
The HYP-OP Study will provide contemporary, real-world data on the burden, clinical correlates, and prognostic significance of OH in hypertensive patients hospitalized in internal medicine wards and may support more consistent implementation of orthostatic BP assessment in routine practice.

Introduction

Orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure (SBP) of at least 20 mmHg and/or a decrease in diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing.[1] Importantly, OH may be asymptomatic or may present with non-specific symptoms (*i.e.*, visual disturbances or lightheadedness), leading to underdiagnosis in routine clinical practice.
The prevalence of OH increases with age and may approach 30% in elderly populations.[2] OH has been associated with impaired quality of life, cognitive decline, falls, major cardiovascular (CV) events.[2-4] and increased mortality. It is frequently observed in patients with heart failure and Parkinson's disease,[4] and it may occur in patients with arterial hypertension (AH), particularly if treated with antihypertensive drugs (*e.g.*, α-blockers and diuretics).[5] AH is both a risk factor and a clinical context in which OH may emerge, especially following intensive BP lowering. Hypertensive patients, particularly the elderly, often have a poor perception of their risk of complications.[6]
Current hypertension guidelines recommend measuring blood pressure (BP) not only in the seated position but also after standing, particularly in elderly patients, in individuals with type 2 diabetes, and in other conditions predisposing to OH.[7]
However, orthostatic BP measurement is not routinely performed in hospitalized patients, and data on OH prevalence and associated conditions in Internal Medicine wards remain limited.
To address this gap, the Federation of Associations of Hospital Internists (FADOI), in collaboration with the Italian Society of Arterial Hypertension (SIIA), designed the HYP-OP Study to evaluate the prevalence, associated clinical conditions, and prognostic impact of OH in hypertensive patients hospitalized in internal medicine wards.

Materials and Methods

Study design and setting

The HYP-OP Study is a national, multicenter, prospective, observational cohort study carried out in approximately 30 Internal Medicine Units across Italy. The study has a non-profit design and does

not include any experimental intervention. All diagnostic procedures and therapeutic decisions are made according to routine clinical practice.
The study consists of two phases: i) during hospitalization, consecutive eligible patients are enrolled and undergo a comprehensive baseline assessment; ii) post-discharge follow-up (FW) at 6, 12, 24, and 36 months after discharge to assess clinical outcomes.
Participating centers enroll consecutive patients during the predefined recruitment period in order to minimize selection bias and enhance representativeness of the Internal Medicine inpatient population.

Study population
Adult patients (≥18 years) with established AH or newly diagnosed AH during hospitalization are eligible. Hypertension is defined according to contemporary European guideline criteria (2018 European Society of Hypertension guidelines), either as a documented diagnosis under antihypertensive treatment or as newly detected elevated BP values meeting guideline thresholds.
To undergo orthostatic BP assessment, patients must be able to stand safely for at least 3 minutes. Patients unable to stand because of clinical instability, severe functional limitation, or other medical contraindications are excluded. Written informed consent is obtained from all participants before to enrollment.

Orthostatic blood pressure assessment
Orthostatic BP measurement is performed according to international consensus criteria,[1] using a standardized protocol shared across participating centers.
After at least 5 minutes of rest in the seated position, SBP and DBP, as well as heart rate, are recorded. Patients are then assisted to stand, and BP and heart rate values are measured again after 1 minute and 3 minutes in the standing position. Measurements are obtained using validated automated devices or calibrated sphygmomanometers routinely used at each participating center.
OH is defined as a decrease in SBP of at least 20 mmHg and/or a decrease in DBP of at least 10 mmHg occurring within 3 minutes of standing.[1] Both symptomatic and asymptomatic forms are recorded. In addition, cases of OH, defined as an abnormal increase in BP upon standing according to available literature definitions, are documented for exploratory analyses.

Baseline data collection
All data are entered into a centralized, password-protected electronic case report form. Each participant is identified by a unique numerical code to ensure anonymity. No directly identifiable personal information is stored.
Demographic variables and a detailed medical history are collected from clinical records, with particular attention to comorbidities (Table 1).
Global comorbidity burden is quantified using the Charlson Comorbidity Index. The history of falls in the previous year and lifestyle habits are also collected.
Medication use at admission is documented in detail, with a focus on antihypertensive therapy. The number of antihypertensive drugs and their pharmacological classes (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, diuretics, α-blockers, and others) are recorded in order to evaluate their potential association with orthostatic BP changes.
Cognitive function is assessed using the Mini-Mental State Examination, and the total score (range 0-30) is recorded. When appropriate, the score is adjusted for educational level according to standard recommendations.
Frailty and lower extremity physical performance are evaluated using the Short Physical Performance Battery (SPPB), which includes balance testing, a 4-meter gait speed assessment, and a repeated chair-stand test. The total SPPB score ranges from 0 to 12, with lower scores indicating greater frailty and poorer physical performance.
Laboratory data obtained as a part of routine clinical care are recorded, including hemoglobin, blood glucose, platelet count, alanine aminotransferase, aspartate aminotransferase, serum creatinine, uric

acid, triglycerides, HDL cholesterol, and LDL cholesterol. When available, kidney function is further characterized by the estimated glomerular filtration rate.

Follow-up procedures and outcome assessment

FW assessments are scheduled at 6, 12, 24, and 36 months after the index hospitalization. FW information is collected during outpatient visits or via structured telephone interviews conducted by trained investigators.

During FW, the occurrence of falls, major CV events (including stroke, transient ischemic attack, myocardial infarction, and clinically significant arrhythmias), and all-cause mortality is recorded. When feasible, events are recorded, verifying hospital documentation or medical records.

Sample size and statistical analysis

Based on previous evidence suggesting a prevalence of OH of approximately 12% in comparable populations,[3] a sample size of 1000 patients allows a reliable estimation of prevalence within a narrow confidence interval. This sample size also ensures adequate statistical power (80% with a two-sided α level of 0.05) to perform multivariate logistic regression analyses, including up to 10-15 independent items, in line with conventional events-per-variable recommendations.

Continuous variables will be expressed as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables will be presented as absolute numbers and percentages. Comparisons between patients with and without OH will be performed using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Multivariate logistic regression analysis will be used to identify independent predictors of OH. Variables considered clinically relevant and/or significantly associated with OH in univariate analysis will be entered into the model. Results will be reported as odds ratios with 95% confidence intervals. Time-to-event analyses will be conducted to explore the association between OH and long-term outcomes. Kaplan–Meier survival curves and Cox proportional hazards models will be applied where appropriate. A two-tailed $p<0.05$ will be considered statistically significant.

The study protocol was registered on ClinicalTrials.gov (NCT05247060)

Discussion and Conclusions

OH is a clinically relevant but frequently underrecognized condition in hypertensive patients hospitalized in Internal Medicine wards. Although diagnostic criteria are well established,[1] OH assessment remains inconsistently implemented in routine practice.

The HYP-OP Study was specifically designed to address this knowledge gap by applying a standardized orthostatic BP measurement protocol in a large, multicenter cohort of hypertensive inpatients. This is particularly pertinent because internal medicine patients are typically older and characterized by multimorbidity and polypharmacy, all of which may affect orthostatic BP regulation.

Beyond estimating prevalence, HYP-OP aims to identify the main clinical factors independently associated with OH. The comprehensive collection of demographics, clinical, laboratory, pharmacological, cognitive, and functional data variables will enable robust multivariate models to clarify which factors are true predictors rather than simple correlates. In particular, the study will explore the role of age, sex, comorbidity burden, frailty status, cognitive impairment, and specific antihypertensive drug classes in predisposing to OH. Identifying these determinants is essential to move from a merely descriptive approach to a more predictive and clinically actionable framework.

The clinical relevance of OH extends beyond hemodynamic variability. Previous evidence has linked OH to falls, CV and cerebrovascular events, cognitive decline, and overall mortality.[2-4] However, data specifically derived from hospitalized internal medicine populations remain limited. The limitations of this study may be primarily those of a real-world observational study: the groups observed may be influenced by the context and differ in clinical, behavioral, or sociodemographic characteristics; these studies may suggest associations, but cannot definitively demonstrate causal

relationships. Through its longitudinal FW design, HYP-OP will evaluate the short- and long-term prognostic impact of OH in this high-risk population. The occurrence of falls, major CV events (including stroke, myocardial infarction, and arrhythmias), and all-cause mortality will be systematically assessed at 6, 12, 24, and 36 months. This approach will clarify whether the presence of OH is merely a marker of frailty and comorbidity or an independent predictor of adverse outcomes both in the short term and over longer FW.

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Table 1. General characteristics of patients collected in the HYP-OP Study, demographic variables, clinical and comorbid conditions.

Demographic and general characteristics
Age
Gender (female /male)
Coming from (home – nursing-home)
Height and body weight (to compute body mass index)
Marital Status
Presence of caregiver
Falls in the last year
Alcohol abuse
Years of schooling
Employment status (active or retired)
Charlson index
Short Physical Performance Battery (SPPB) score
Mini-Mental State Examination (MMSE) score
In-hospital sitting blood pressure and heart rate
Systolic blood pressure
Diastolic blood pressure
Heart rate
Symptoms
Visual disturbances
Disturbances of consciousness
Difficulty in maintaining an upright position
Dizziness
Other
Neuropsychiatric comorbidities
Major depression
Alzheimer's disease
Parkinson's disease
Others neuropsychiatric comorbidity
Respiratory comorbidities/diseases
Asthma
Chronic obstructive pulmonary disease
Others respiratory comorbidities/diseases
Cardiovascular comorbidities
Peripheral arterial disease
Ischemic heart disease
Stroke
Transient ischemic attack
Heart failure
Others cardiovascular comorbidity
Metabolic comorbidities
Type 1 diabetes
Type 2 diabetes
Hypothyroidism
Hyperthyroidism
Others metabolic comorbidity
Gastro-pancreatic comorbidities
Cirrhosis of the liver
Chronic inflammatory disease
Peptic ulcer
Other gastro-pancreatic comorbidity
Osteoarticular comorbidities
Rheumatoid arthritis
Osteoporosis
Others osteoarticular comorbidity
Oncological comorbidities
Local
Metastatic
Other comorbidities
Chronic kidney disease
Mild
Moderate IIIa
Moderata IIIb
Serious
Anemia