ORIGINAL ARTICLE

Orthostatic Changes in Blood Pressure and Mortality in the Elderly: The Pro.V.A Study

Nicola Veronese,[1] Marina De Rui,[1] Francesco Bolzetta,[1] Sabina Zambon,[2,3] Maria Chiara Corti,[4] Giovanella Baggio,[5] Elena Debora Toffanello,[1] Stefania Maggi,[3] Gaetano Crepaldi,[3] Egle Perissinotto,[6] Enzo Manzato,[1,3] and Giuseppe Sergi[1]

BACKGROUND
An extensive, albeit contrasting literature has suggested a possible role for orthostatic hypotension as a risk factor for cardiovascular (CVD) and non-CVD mortality, while no data are available for orthostatic hypertension. We investigated whether orthostatic changes in blood pressure (BP) were associated with any increased risk of all-cause, CVD or non-CVD mortality in a group of elderly people.

METHODS
Two thousand seven hundred and eighty six community-dwelling older participants were followed for 4.4 years. Participants were grouped according to whether they had a drop ≤20 mm Hg in systolic, or ≤10 mm Hg in diastolic BP (orthostatic hypotension), an increase in mean orthostatic systolic BP ≥20 (orthostatic hypertension), or normal changes within 3 minutes of orthostatism.

RESULTS
During follow-up, 640 subjects died, 208 of them for CVD-related reasons. Adjusted Cox's regression analysis revealed that, compared with normal changes, orthostatic hypertension was associated with higher all-cause (HR = 1.23; 95% CI: 1.02–1.39) and CVD-related mortality (HR = 1.41; 95% CI: 1.08–1.74), while orthostatic hypotension was only associated with a higher non-CVD mortality (HR = 1.19; 95% CI: 1.01–1.60). Orthostatic hypertension emerged as a predictor of all-cause mortality for: participants over 75 years old; participants with a BMI below 25 kg/m^2; participants with no CVD or disabilities; and those taking less than three medications. Orthostatic hypertension also predicted CVD-related mortality in individuals with no hypertension, heart failure, coronary artery disease, or atrial fibrillation.

CONCLUSIONS
Orthostatic hypertension and hypotension both seem to be relevant risk factors for mortality in the elderly, orthostatic hypertension correlating with all-cause and CVD-related mortality and orthostatic hypotension with non-CVD mortality.

Keywords: blood pressure; cardiovascular disease; elderly; hypertension; orthostatic hypertension; orthostatic hypotension; mortality.

doi:10.1093/ajh/hpv022

Orthostatic blood pressure dysregulation is common among older people owing to the aging process itself as well as to dysautonomia due to comorbidities such as Parkinson's disease, cardiovascular diseases (CVD) or diabetes, and the use of medication (such as antihypertensive agents and benzodiazepines).

The most often studied orthostatic blood pressure dysregulation is orthostatic hypotension, which is identified in approximately 20–30% of individuals over 65 years of age[1,2] and is associated with an increase CVD unrelated mortality.[3–6] Extensive research has also tended (with some exceptions) to support a role for orthostatic hypotension as a risk factor for CVD in the elderly.[7–9] On the contrary orthostatic hypertension, has been less thoroughly analyzed.[10] It seems to affect about 10% of older people, but its reported prevalence varies because different criteria have been adopted to define it.[11] Recent researches point to orthostatic hypertension as an emerging hemodynamic cardiovascular risk factor, particularly in older people with essential hypertension.[10,12] The condition seems to be associated with more severe organ damage and a greater risk of clinical and subclinical CVD events.[11,12] To the best of our knowledge, no published data are available on the association between orthostatic hypertension and mortality.

Based on these premises, we hypothesized that not only orthostatic hypotension, but also orthostatic hypertension may be associated to a higher risk of mortality.

Correspondence: Nicola Veronese (ilmannato@gmail.com).

Initially submitted November 10, 2014; date of first revision November 24, 2014; accepted for publication January 22, 2015; online publication March 11, 2015.

[1]Geriatrics Section, Department of Medicine—DIMED, University of Padova, Padova, Italy; [2]Department of Medicine—DIMED, Clinica Medica 1, University of Padova, Padova, Italy; [3]National Research Council, Neuroscience Institute, Padova, Italy; [4]Division of Health Care Planning and Evaluation of the Regione Veneto, Venice, Italy; [5]Internal Medicine Division, Azienda Ospedaliera, Padova, Italy; [6]Department of Cardiac, Thoracic and Vascular Sciences—Biostatistics, Epidemiology and Public Health Unit, University of Padova, Padova, Italy
Veronese and De Rui equally contributed to this study.

The aim of the present study was thus to examine whether orthostatic changes in blood pressure (defined as orthostatic hypo- and hypertension) were associated with any increased risk of all-cause, CVD, or non-CVD mortality in a representative group of elderly men and women over a lengthy follow-up (4.4 years).

METHODS

Data source and subjects

The data for this analysis were drawn from the *Progetto Veneto Anziani* (Pro.V.A.), an observational cohort study on the Italian population aged ≥65 years that included 3,099 age- and sex-stratified Caucasian participants (1,854 women and 1,245 men) randomly selected between 1995 and 1997 using a multistage stratified method. Sampling procedures and data collection methods have been described elsewhere.[13] Trained physicians and nurses examined participants at various clinics. The present study concerns the information collected on the mortality rate over a mean 4.4 years (±1.2 SD) of follow-up. Copies of the official death certificates were obtained for all deceased participants. CVD-related mortality was recorded using the codes from 390 to 459 of the International Classification of Diseases—9th Revision, 2002 during the follow-up; any other causes of mortality were classified as non-CVD. Among the 3,099 subjects initially considered, no blood pressure data in an orthostatic position were available for 128, and for another 185 no information about death was available, so 2,786 participants were included in the final analysis.

The ethical committees of Padua University and the Veneto Region's Local Health Units (USSL) n. 15 and n. 18 approved our study protocol, and participants gave their written informed consent to the study.

Clinical data

Participants were examined at the city hospitals by trained physicians and nurses. A face-to-face interview was used to collect information on their usual physical activity, smoking habits, and number and type of drugs used. Regular physical activity was defined as ≥4 hour/week in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing, or physical exercising). Smoking habits were dichotomized as "never/former smoker" (if a subject had given up smoking at least a year earlier) vs. "current smoker." Body weight and height were measured by trained physicians and the body mass index (BMI, kg/m^2) was calculated.

Any diseases were assessed by board-certified physicians, who considered all the clinical details collected for each participant in the study (clinical history, symptoms self-reported by means of standardized questionnaires, medical and hospital records, blood tests), and conducted a physical examination. Diabetes mellitus was defined as at least the presence of one of the following criteria: fasting plasma glucose ≥7.0 mmol/l, HbA1c ≥6.5%, use of glucose-lowering drugs, history of 2 hours post-load glucose ≥11.1 mmol/l. Cognitive function was assessed with the 30-item Mini-Mental State Examination (MMSE), and mood with the Geriatric Depression Scale (GDS) using cut-offs of 24 and 11 for a diagnosis of cognitive impairment and depression, respectively.[14,15]

Multidimensional assessment

A multidimensional assessment was conducted by physicians expert in geriatric medicine. Functional status was assessed using the ADL (activities of daily living) score.[16] Disability was classified as "able" (i.e., an ADL score = 6) vs. "disabled" in ADL.

The Short Physical Performance Battery (SPPB) was obtained from three objective physical function tests: the tandem test, gait speed, and chair stands time.[17] Each test was scored from 0 (inability to complete the test) to 4 (highest level of performance). The scores obtained in all three tests were pooled to form a composite score of 0–12, higher scores reflecting better physical function.

Definition of orthostatic hypertension and hypotension

All blood pressure (BP) measurements were taken by a trained nurse in the morning. The mid-point of the right upper arm was ascertained by measuring the length from the tip of the shoulder to the tip of the elbow and dividing this length by 2. The tape was wrapped around the straightened arm at the midpoint identified and the cuff was checked to ensure that it was neither too tight nor too loose. The measurement was recorded to the nearest 0.1 cm and repeated twice if measurements differed by less than 0.8 cm. An appropriate size of cuff was chosen, based on the circumference of the participant's arm, i.e., small (<24 cm), normal (24–32 cm), and large (33–41 cm). Clinostatic BP was measured in the right arm three times with 30-second intervals between measurements, using a mercury sphygmomanometer (Erkameter 300), in participants who had been supine for at least 5 minutes, taking the mean value as the clinostatic measure.[18] Hypertension was defined as the presence of systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or current use of antihypertensive medications.[18] Pulse pressure was defined as the difference between systolic and diastolic BP.

Orthostatic BP and heart rate were then measured after 1 and 3 minutes of orthostatism. In accordance with the guidelines of the Consensus Committee of the American Autonomic Society, and the American Academy of Neurology, orthostatic hypotension was defined as a drop of at least 20 mm Hg in systolic blood pressure, or at least 10 mm Hg in diastolic blood pressure in one of the two measurements.[19] Since no formal consensus exists on how orthostatic hypertension should be defined, we adopted the most often-used definition for this condition, i.e., an increase in systolic blood pressure in excess of 20 mm Hg calculated as the mean of the systolic blood pressure measurements obtained during orthostatism minus the supine blood pressure before standing (definitive diagnosis).[11]

Laboratory data

Venous blood samples were obtained after an overnight fast for biochemical tests, which were performed at the city

hospital's central laboratory using standard, quality-controlled procedures.

Serum creatinine levels were measured using the Jaffe reaction with the Roche/Hitachi auto analyzer (Roche Diagnostic GmbH, Mannheim, Germany) calibrated with the uncompensated method, while the estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. Total cholesterol levels were assessed using the enzymatic method.

Statistical analyses

Participants' characteristics were summarized using means (±SDs) for continuous variables, and counts and percentages for categorical variables. Means and proportions were compared between participants grouped according to the changes in their orthostatic blood pressure. Age- and gender-adjusted *P* values were calculated as follows: for continuous variables the differences between the means of the covariates for orthostatic changes in blood pressure were analyzed using analysis of variance (ANOVA) with Bonferroni's correction; logistic regression was applied for categorical variables.

The incidence rate for mortality was calculated as the number of new cases of death per 1,000 persons per year during the follow-up. Cox's proportional hazard models were used to assess associations between orthostatic changes in blood pressure and mortality. Known factors associated with orthostatic blood pressure and mortality in older people were considered for inclusion in the analysis. To explore whether a variable should be included as a predictor in the fully adjusted models the log-rank test of equality across strata was performed for all the categorical variables and Cox's univariate proportional hazards regression for all the continuous variables. The predictors included in the fully adjusted model were all the variables reaching a $P < 0.20$ in the univariate analyses. Collinearity among covariates was quantified using the variance inflation factor (VIF) taking a cut-off of 2. We therefore excluded any presence of atrial fibrillation, which was included in the definition of CVD instead. In the multivariate analysis, a stepwise selection was used to obtain the set of variables most effective in predicting the dependent variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to compare mortality rates across orthostatic changes in blood pressure taking participants with normal changes for reference. We conducted several sensitivity analyses stratifying for clinical factors independently associated with mortality in the final model, or known CVD risk factors in the case of CVD-related mortality to see if the orthostatic changes in blood pressure can depend on any medical or other conditions.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, IL). All statistical tests were two-tailed and statistical significance was assumed for a *P*-value <0.05.

RESULTS

Baseline characteristics

The sample of 2,786 community-dwelling elderly were a mean 76.0 ± 7.6 years old (range: 65–103); 59% were females; and the mean BMI was 27.6 ± 4.6 kg/m^2. The participants scored less than 6 for ADL amounted for the 43.4% of the sample. In the sample as a whole, the prevalence of orthostatic hypotension and hypertension was 9.3% and 19.5%, respectively. The mean clinostatic systolic and diastolic BP was 153.4 ± 21.5 and 82.9 ± 11.2 mmHg, while changes in the orthostatic position amounted to a mean −1.1 ± 13.0 mm Hg (range: −53 to 42) and 3.8 ± 7.7 mm Hg (range: −62 to 44) for systolic and diastolic blood pressure, respectively.

As shown in Table 1, participants with orthostatic hypertension were significantly younger than those with orthostatic hypotension ($P < 0.0001$), but of similar age to those with normal BP changes ($P = 0.89$). No significant differences emerged for gender (*P* for overall comparisons = 0.25).

Compared with those with normal orthostatic changes in BP, participants with orthostatic hypertension were less likely to be smokers ($P = 0.01$) or to have congestive heart failure ($P = 0.03$), or COPD ($P = 0.01$), while those with orthostatic hypotension had more frequently been diagnosed with cognitive impairment ($P = 0.03$), Parkinson's disease ($P = 0.005$), or peripheral artery disease ($P = 0.01$). Participants with orthostatic hypotension were also more frequent users of drugs for Parkinsonism (*P* for overall comparisons = 0.01), calcium channel blockers (*P* for overall comparisons = 0.005), or nitrates (*P* for overall comparisons = 0.004) than the other two groups. Finally, participants with orthostatic hypotension had significantly lower SPPB scores than the other two groups ($P = 0.008$ for both comparisons).

As for the clinostatic BP parameters, participants with orthostatic hypertension had significantly lower systolic BP values than those with orthostatic hypotension ($P < 0.0001$), and the lowest clinostatic diastolic BP value (*P* for overall comparisons < 0.0001), while those with orthostatic hypotension had the highest pulse pressure value (*P* for overall comparisons < 0.0001) (Table 1).

Follow-up data

Over a period of 4.4 years, 640 participants died, 208 of them for CVD-related reasons. Compared to other two groups, the incidence mortality rate was significantly higher in those with orthostatic hypotension for all-cause (Cox's regression analysis; $P = 0.02$) and CVD ($P = 0.04$), while for mortality unrelated to CVD there was a trend that fell short of statistical significance ($P = 0.17$) (Table 2).

Taking participants with normal pressure changes in the orthostatic position for reference and adjusting for potential confounders, orthostatic hypertension was associated with a higher all-cause mortality (HR = 1.23; 95% CI: 1.02–1.39; $P = 0.03$) and CVD-related mortality (HR = 1.41; 95% CI: 1.08–1.74; $P = 0.02$), while orthostatic hypotension was only associated with a higher non-CVD mortality (HR = 1.19; 95% CI: 1.01–1.60; $P = 0.047$) (Table 2).

Figures 1 and 2 show a stratification for some conditions associated with all-cause mortality in older people. Orthostatic hypertension emerged as a predictor of all-cause mortality for participants aged >75 years, for those with a BMI <25 kg/m^2, without CVD or disabilities at baseline, and for those taking less than three medications. Moreover,

Table 1. Participants' characteristics by changes in their orthostatic blood pressure

Variables	Orthostatic hypotension (*n* = 261)	Normal changes (*n* = 1,981)	Orthostatic hypertension (*n* = 544)	Orthostatic hypotension vs. normal changes, *P* value	Orthostatic hypertension vs. normal changes, *P* value	Orthostatic hypertension vs. orthostatic hypotension, *P* value	Overall comparison, *P* value[a]
Age (years)	77.66 (7.83)	75.83 (7.60)	75.53 (7.36)	0.001	0.89	0.001	<0.0001[b]
Female sex (%)	57.9	58.5	61.6	0.94	0.20	0.37	0.25[b]
BMI (kg/m^2)	26.76 (4.40)	27.77 (4.68)	27.18 (4.27)	0.08	1.00	1.00	0.40
SPPB (points)	6.91 (3.82)	7.95 (3.58)	8.06 (3.50)	0.008	1.00	0.008	0.006
Current smokers (%)	10.0	9.8	6.3	0.55	0.01	0.02	0.01
Physical activity ≥ 4 h/week (%)	21.1	23.8	24.6	0.62	0.75	0.53	0.42
Disability (%)	49.8	42.7	42.8	0.29	0.74	0.48	0.54
Blood pressure measurements							
Clinostatic systolic BP (mm Hg)	162.56 (21.90)	153.06 (21.69)	152.28 (21.14)	<0.0001	1.00	<0.0001	<0.0001
Clinostatic diastolic BP (mm Hg)	85.98 (11.50)	83.20 (11.04)	80.30 (11.38)	<0.0001	<0.0001	<0.0001	<0.0001
Pulse pressure (mm Hg)	76.58 (16.98)	69.08 (16.96)	72.77 (17.41)	<0.0001	<0.0001	<0.0001	<0.0001
Clinostatic heart rate (bpm)	71.59 (11.94)	71.29 (11.85)	72.30 (12.60)	1.00	0.26	0.26	0.22
1 min orthostatic systolic BP (mm Hg)	135.25 (27.22)	147.55 (23.44)	159.82 (24.54)	<0.0001	<0.0001	<0.0001	<0.0001
1 min orthostatic diastolic BP (mm Hg)	79.12 (15.22)	84.72 (11.96)	94.14 (13.25)	<0.0001	<0.0001	<0.0001	<0.0001
1 min orthostatic heart rate (bpm)	79.01 (13.07)	78.34 (13.09)	81.24 (13.76)	1.00	<0.0001	0.04	<0.0001
3 min orthostatic systolic BP (mm Hg)	143.09 (23.07)	154.19 (22.08)	168.30 (23.69)	<0.0001	<0.0001	<0.0001	<0.0001
3 min orthostatic diastolic BP (mm Hg)	82.12 (13.41)	85.97 (11.36)	94.83 (12.85)	<0.0001	<0.0001	<0.0001	<0.0001
3 min orthostatic heart rate (bpm)	77.53 (13.33)	76.15 (12.59)	78.65 (13.78)	0.55	<0.0001	0.52	<0.0001
Mean orthostatic heart rate (bpm)	78.27 (12.72)	77.25 (12.39)	79.94 (13.26)	0.97	<0.0001	0.16	<0.0001
Medical conditions							
Cognitive impairment (%)	12.6	7.6	6.1	0.03	0.33	0.01	0.047
Parkinson disease (%)	2.7	1.0	0.9	0.005	0.89	0.12	0.02
CVD (%)	29.1	21.8	22.2	0.05	0.67	0.17	0.41
Congestive heart failure (%)	8.4	6.8	4.2	0.82	0.03	0.07	0.045

Table 1. *Continued*

Variables	Orthostatic hypotension (*n* = 261)	Normal changes (*n* = 1,981)	Orthostatic hypertension (*n* = 544)	Orthostatic hypotension vs. normal changes, *P* value	Orthostatic hypertension vs. normal changes, *P* value	Orthostatic hypertension vs. orthostatic hypotension, *P* value	Overall comparison, *P* value[a]
Coronary artery disease (%)	10.7	7.4	6.3	0.08	0.38	0.04	0.06
Stroke (%)	4.6	3.9	4.2	0.81	0.66	0.94	0.79
Peripheral artery disease (%)	27.6	18.9	19.3	0.01	0.71	0.15	0.18
Atrial fibrillation (%)	3.1	4.2	4.0	0.28	0.88	0.38	0.51
Hypertension (%)	82.8	73.4	73.8	0.003	0.80	0.62	0.07
Cancer (%)	10.0	7.4	6.8	0.20	0.64	0.16	0.22
Diabetes (%)	22.6	15.0	16.9	0.02	0.27	0.16	0.23
COPD (%)	10.4	10.3	5.5	0.70	0.01	0.03	0.02
Hip fracture (%)	3.1	2.8	3.9	0.99	0.17	0.40	0.26
Depression (%)	40.2	36.0	36.0	0.28	0.94	0.37	0.38
Biohumoral tests							
Total cholesterol (mg/dl)	229.46 (43.99)	229.94 (46.00)	233.60 (41.20)	1.00	0.53	1.00	0.40
eGFR (ml/min)	66.08 (19.97)	69.35 (18.60)	69.05 (17.77)	0.21	1.00	0.52	0.19
Drugs							
Number of drugs	3.65 (1.88)	3.38 (1.90)	3.31 (1.94)	0.13	0.10	0.30	0.26
Benzodiazepines (%)	24.3	24.0	26.4	0.97	0.30	0.53	0.50
Anti-Parkinson drugs (%)	5.4	2.0	1.6	0.01	0.004	0.61	0.01
Statins (%)	2.7	2.6	2.5	0.74	0.84	0.67	0.67
Low-dose aspirin (%)	22.5	13.7	16.0	0.002	0.20	0.09	0.35
ACE inhibitors (%)	28.4	27.9	34.0	0.89	0.01	0.15	0.045
Diuretics (%)	43.2	51.1	41.4	0.98	0.81	0.89	0.89
Beta-blockers (%)	7.7	5.2	6.3	0.05	0.38	0.27	0.55
Calcium channel blockers (%)	31.1	23.7	20.3	0.03	0.14	0.004	0.005
Central anti-hypertensive (%)	6.8	3.2	4.7	0.01	0.12	0.29	0.59
Vasodilators (%)	13.5	10.2	13.1	0.29	0.06	0.73	0.39
Nitrates (%)	16.2	9.9	7.4	0.02	0.13	0.002	0.004
Any anti-hypertensive (%)	66.7	56.1	59.0	0.01	0.17	0.16	0.52

Numbers are mean values (and SDs) or percentages (%), as appropriate.

Abbreviations: BMI, body mass index; SPPB, short physical performance battery; BP, blood pressure; CVD, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

[a]Unless otherwise specified, *P* values are adjusted for age and gender using a general linear model (with the Bonferroni's correction) or logistic regression, as appropriate.

[b]Not adjusted for age or gender.

Table 2. Association between changes in orthostatic blood pressure and mortality: the PRO.V.A. study

	No. of events	No. of people	Incidence rate (per 1,000 person-years) (95% CI)	Unadjusted hazard ratio (95% CI)	*P* value	Fully adjusted model (HR with 95% CI)	*P* value
All-cause mortality							
Normal change	431	1,981	51 (29–73)	1 [reference]		1 [reference]	
Orthostatic hypotension	83	261	81 (33–129)	1.56 (1.22–1.99)	<0.0001	1.13 (0.88–1.45)	0.35
Orthostatic hypertension	126	544	54 (12–96)	1.05 (0.85–1.28)	0.37	1.23 (1.02–1.39)	0.03
CVD mortality							
Normal change	137	1,981	16 (0–32)	1 [reference]		1 [reference]	
Orthostatic hypotension	26	261	25 (0–78)	1.52 (0.91–2.23)	0.13	0.94 (0.59–1.49)	0.79
Orthostatic hypertension	45	544	19 (0–52)	1.14 (0.80–1.61)	0.47	1.41 (1.08–1.74)	0.02
Non-CVD mortality							
Normal change	294	1,981	35 (14–56)	1 [reference]		1 [reference]	
Orthostatic hypotension	57	261	56 (0–116)	1.62 (1.21–2.17)	0.001	1.19 (1.01–1.60)	0.047
Orthostatic hypertension	81	544	35 (0–75)	1.00 (0.78–1.29)	0.99	1.08 (0.84–1.40)	0.54

Unless otherwise specified, data are presented as hazard ratios and 95% confidence interval. Fully-adjusted model included: age (continuous); gender; BMI (< or ≥ 25); presence/history of: diabetes, cardiovascular diseases, COPD, cancer, cognitive impairment; serum total cholesterol (as continuous); smoking status (current vs. former-never); number of drugs; SPPB; presence of frailty (frail vs. pre-frail and not frail); clinostatic systolic and diastolic BP (as continuous).

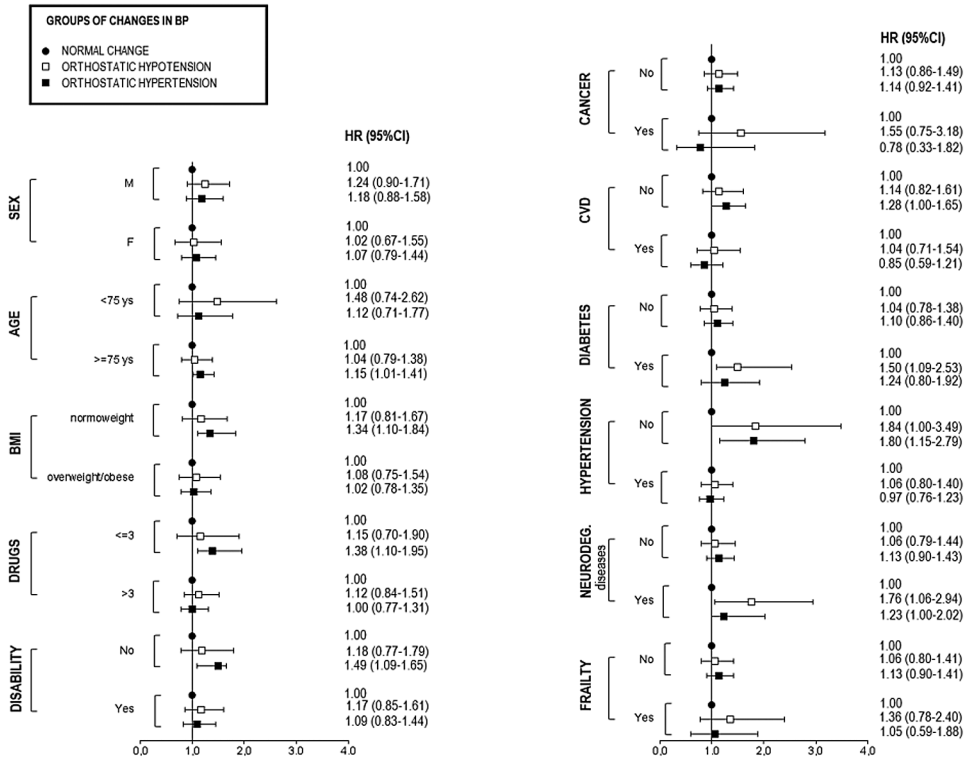

Figure 1. Adjusted hazard ratios (for the same covariates as in Table 2) for all-cause mortality by change in orthostatic blood pressure in relation to several independent factors for mortality: the PRO.V.A. study. *Notes*: Black circles indicate orthostatic hypotension; empty circles indicate orthostatic hypertension; squares (reference) indicate normal orthostatic changes in blood pressure. The HRs were drawn with the corresponding 95% CI. BMI, body mass index; CVD, cardiovascular disease.

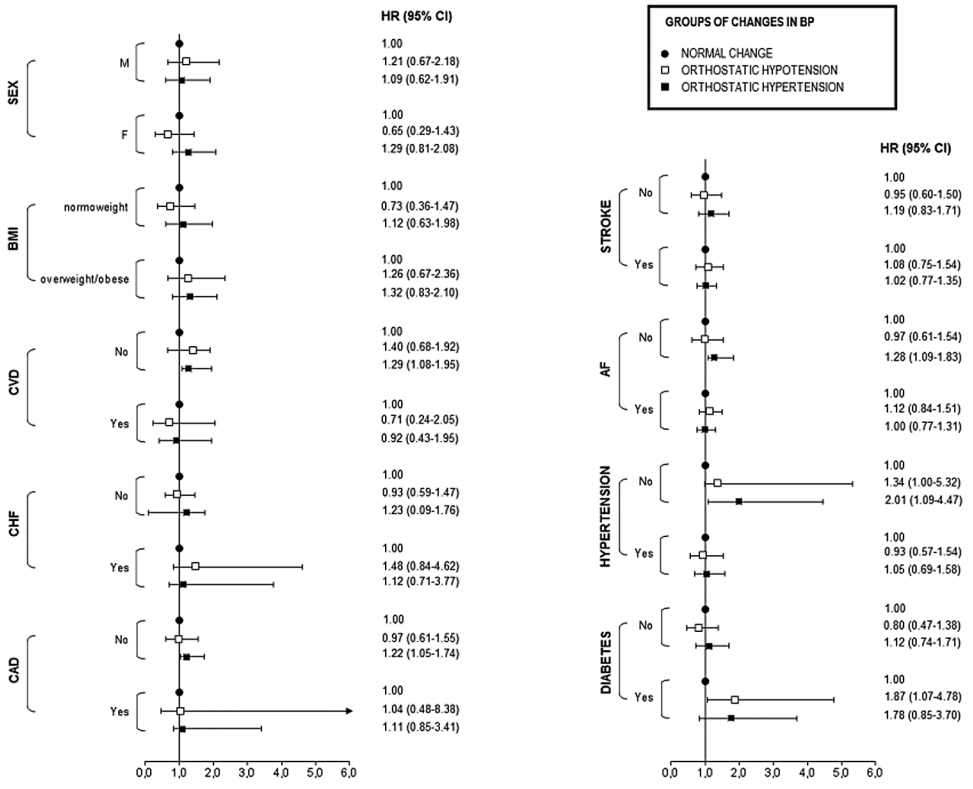

Figure 2. Adjusted hazard ratios (for the same covariates as in Table 2) for CVD-related mortality by change in orthostatic blood pressure in relation to some CVDs or risk factors: the PRO.V.A. study. *Notes*: Black circles indicate orthostatic hypotension; empty circles indicate orthostatic hypertension; squares (reference) indicate normal orthostatic changes in blood pressure. The HRs were drawn with the corresponding 95% CI. BMI, body mass index; CVD, cardiovascular disease; CHF, congestive heart failure; CAD, coronary artery disease; AF, atrial fibrillation.

orthostatic hypertension predicted CVD-related mortality in individuals with no hypertension, heart failure, stroke, coronary artery disease, or atrial fibrillation at baseline. Orthostatic hypotension was a significant predictor of mortality in participants with diabetes and neurodegenerative diseases, and in those without high blood pressure (Figures 1 and 2).

DISCUSSION

Our large population-based prospective study found orthostatic hypertension associated with all-cause and CVD-related mortality, and orthostatic hypotension with non-CVD mortality.

The association between orthostatic hypertension and mortality is particularly noteworthy, since that clinicians are usually much more preoccupied of avoiding orthostatic hypotension for its well-known direct consequences on elderly people as syncope and falls, and may interpret any increase in orthostatic pressure as a favorable event.

The association between orthostatic hypertension and mortality became evident only after adjustment for potential confounders, suggesting that in these people the negative effect of orthostatic hypertension is counterbalanced by other conditions (like being in better physical shape, and with a lower prevalence of other potentially fatal conditions) with protective effect toward mortality. Surprisingly, orthostatic hypertension emerged as a significant risk factor for CVD-related mortality in participants with no atrial fibrillation, stroke, coronary artery disease, or congestive heart failure at baseline. In the majority of the studies available in the literature, the association between orthostatic hypertension and cardiovascular morbidity has been investigated only in already diagnosed hypertensive subjects.[11,20,21] Instead, the findings of the present study highlight the importance of diagnosing orthostatic hypertension especially in subjects apparently in good health status and without established cardiovascular comorbidities. These results seem to support the hypothesis of Kario who considered orthostatic hypertension as a form of prehypertension.[22]

To explain the reasons why orthostatic hypertension emerged as a risk for CVD-related mortality only in subjects free from cardiovascular diseases at baseline, we can hypothesize that CVD are *per se* at high risk of death, and this may reduce the importance of orthostatic changes in blood pressure as risk factor for mortality. Moreover, it is also possible that elderly people with already CVD at baseline use more frequently drugs able to lower orthostatic blood pressure leading to a bias in the evaluation of orthostatic hypertension. However, taken together, these findings suggest that orthostatic hypertension is an early CVD risk factor in the elderly, consistently with studies finding this condition associated with both subclinical and clinical forms of CVD.[8]

The mechanisms linking orthostatic hypertension and CVD are not fully understood, but they seem to include systemic hemodynamic atherosclerotic syndrome (SHAS).[23] In

patients with SHAS, both large and small systemic arteries are overloaded due to a pulsatile hemodynamic stress that may contribute to the progression of the atherosclerotic process. In older people, concomitant conditions (such as stiffer large arteries and an impaired autoregulation of small arteries) lead to a lower pulse wave attenuation and a consequent increase in hemodynamic stresses, with chronic damage to certain vital organs. Advanced vascular disease and ischemic peripheral organ damage activate the renin-angiotensin system, giving rise to an increased sympathetic activity and a decreased baroreceptor sensitivity with a consequent increase in orthostatic heart rate (as shown in our study), and exacerbating the chronic damage to peripheral organs. Finally, orthostatic hypertension may also be associated with other CVD risk factors not investigated here, such as masked hypertension.[24]

As for orthostatic hypotension, we found a higher risk of all-cause mortality that disappeared after adjusting for several potential confounders. This picture is consistent with a recent Italian study in which the role of orthostatic hypotension as a risk factor for CVD no longer existed after correcting for some confounders.[7] Taken together, these findings suggest that orthostatic hypotension should be considered a risk factor for mortality or CVD more for the conditions associated with it than *per se.* Unlike some other studies,[4,25] we found no significant association between orthostatic hypotension and CVD-related mortality. Possible explanations for this discrepancy lie in that we considered participants with a higher orthostatic blood pressure as a separate entity instead of including them in the reference group, and in the number and type of covariates for which we adjusted our analysis. On the other hand, our findings as regards non-CVD mortality are consistent with a recent meta-analysis in which orthostatic hypotension was found related mainly to non-CVD mortality.[3,26,27] This would reinforce the conviction that this condition is more important because of other outcomes related to mortality in old age, such as falls and fractures.

Some limitations should be considered when interpreting our results. The first concerns the use of standing blood pressure measurements, a first-line test for identifying orthostatic changes in blood pressure; other tests (e.g., head up tilting) would be more accurate in diagnosing orthostatic blood pressure changes. Another shortcoming lies in that we only conducted one session of clinostatic and orthostatic BP measurements, which may not be optimal for defining orthostatic hypo- or hypertension in an elderly cohort.[28] Another limitation is that we only measured orthostatic hemodynamic parameters at 1 and 3 minutes, whereas orthostatic hypotension is known to develop later in many people aged >65 years.[29] Finally, we have to consider the possibility of a type II error in our analyses because of the small proportion of participants with orthostatic hypotension, probably due to a survival bias (i.e., subjects with orthostatic hypotension died before the survey, given that this condition is associated with several forms of CVD in our study); this could reduce the power of our results.

In conclusion, orthostatic hypertension and hypotension both seem to be relevant risk factors for mortality in the elderly, the former correlating with all-cause and CVD-related mortality, and the latter with non-CVD mortality. More research is needed to confirm the role of orthostatic hypertension as a risk factor for CVD in the elderly, and to ascertain whether treating this condition can lower the CVD-related mortality rate.

ACKNOWLEDGMENTS

We are grateful to all interviewers, nurses, and physicians involved in the work. This work was funded by the Fondazione Cassa di Risparmio di Padova e Rovigo; University of Padova; Azienda Unità Locale Socio Sanitaria 15 and 18 of the Veneto Region; Intramural Research Program of the National Institute on Aging; the Veneto Region Research Project 104/02 (Corti).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; 120:841–847.
2. Veronese N, Bolzetta F, De Rui M, Zambon S, Corti MC, Musacchio E, Baggio G, Crepaldi G, Perissinotto E, Manzato E, Sergi G. Serum 25-hydroxyvitamin D and orthostatic hypotension in old people: the Pro.V.A. study. *Hypertension* 2014; 64:481–486.
3. Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. *Heart* 2014; 100:406–413.
4. Rose KM, Tyroler HA, Nardo CJ, Arnett DK, Light KC, Rosamond W, Sharrett AR, Szklo M. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. *Am J Hypertens* 2000; 13:571–578.
5. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987–1996. *Stroke* 2000; 31:2307–2313.
6. Jones CD, Loehr L, Franceschini N, Rosamond WD, Chang PP, Shahar E, Couper DJ, Rose KM. Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study. *Hypertension* 2012; 59:913–918.
7. Casiglia E, Tikhonoff V, Caffi S, Boschetti G, Giordano N, Guidotti F, Segato F, Mazza A, Grasselli C, Saugo M, Rigoni G, Guglielmi F, Martini B, Palatini P. Orthostatic hypotension does not increase cardiovascular risk in the elderly at a population level. *Am J Hypertens* 2014; 27:81–88.
8. Fedorowski A, Engström G, Hedblad B, Melander O. Orthostatic hypotension predicts incidence of heart failure: the Malmö preventive project. *Am J Hypertens* 2010; 23:1209–1215.
9. Sung SH, Chen ZY, Tseng TW, Lu DY, Yu WC, Cheng HM, Chen CH. Wave reflections, arterial stiffness, and orthostatic hypotension. *Am J Hypertens* 2014; 27:1446–1455.
10. Robertson D. Orthostatic hypertension: the last hemodynamic frontier. *Hypertension* 2011; 57:158–159.
11. Kario K. Orthostatic hypertension—a new haemodynamic cardiovascular risk factor. *Nat Rev Nephrol* 2013; 9:726–738.
12. Eguchi K, Kario K, Hoshide S, Hoshide Y, Ishikawa J, Morinari M, Hashimoto T, Shimada K. Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. *Hypertens Res* 2004; 27:235–241.
13. Corti MC, Guralnik JM, Sartori L, Baggio G, Manzato E, Pezzotti P, Barbato G, Zambon S, Ferrucci L, Minervini S, Musacchio E, Crepaldi G. The effect of cardiovascular and osteoarticular diseases on disability in older Italian men and women: rationale, design, and sample characteristics of the Progetto Veneto Anziani (PRO.V.A.) study. *J Am Geriatr Soc* 2002; 50:1535–1540.

14. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. *Arch Gen Psychiatry* 1983; 40:812.
15. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982; 17:37–49.
16. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; 10:20–30.
17. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; 49:M85–M94.
18. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142–161.
19. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996; 46:1470.
20. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM; ARIC Study Investigators. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. *Hypertension* 2011; 57:167–173.
21. Fan XH, Wang Y, Sun K, Zhang W, Wang H, Wu H, Zhang H, Zhou X, Hui R. Disorders of orthostatic blood pressure response are associated with cardiovascular disease and target organ damage in hypertensive patients. *Am J Hypertens* 2010; 23:829–837.
22. Kario K. Orthostatic hypertension: a measure of blood pressure variation for predicting cardiovascular risk. *Circ J* 2009; 73:1002–1007.
23. Ketch T, Biaggioni I, Robertson R, Robertson D. Four faces of baroreflex failure: hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation* 2002; 105:2518–2523.
24. Barochiner J, Cuffaro PE, Aparicio LS, Alfie J, Rada MA, Morales MS, Galarza CR, Waisman GD. Predictors of masked hypertension among treated hypertensive patients: an interesting association with orthostatic hypertension. *Am J Hypertens* 2013; 26:872–878.
25. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM, Witteman JC. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. *J Am Geriatr Soc* 2008; 56:1816–1820.
26. Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: implications for management of cardiovascular disease. *Am J Hypertens* 2011; 24:135–144.
27. Masaki KH, Schatz IJ, Burchfiel CM, Sharp DS, Chiu D, Foley D, Curb JD. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation* 1998; 98:2290–2295.
28. Weiss A, Grossman E, Beloosesky Y, Grinblat J. Orthostatic hypotension in acute geriatric ward: is it a consistent finding? *Arch Intern Med* 2002; 162:2369–2374.
29. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. *Lancet Neurol* 2008; 7:451–458.