Orthostatic Hypotension Does Not Increase Cardiovascular Risk in the Elderly at a Population Level

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BACKGROUND
The general belief that orthostatic hypotension (OH) predisposes to cardiovascular events is based on sparse and contradictory data, rarely derived from population studies.

METHODS
A total of 1,016 men and women aged ≥65 years was studied in a 12-year epidemiological population-based study. Cardiovascular events were detected in subjects with and without OH (blood pressure (BP) decrease ≥20 mm Hg for systolic or ≥10 mm Hg for diastolic), and Cox analysis was performed including OH as an independent variable.

RESULTS
In univariate analysis, coronary (20.2% vs. 13.1%, P = 0.05), cerebrovascular (13.1% vs. 8.4%, P = 0.05), and heart failure (HF) events (20.2% vs. 13.8%, P = 0.03) were apparently more incidental in subjects with OH than in those without OH. Nevertheless, after adjusting for age, gender, and systolic BP as confounders, OH did not act as a cardiovascular predictor (relative risk for cerebrovascular events 1.33, 95% confidence interval (CI), 0.78–2.2, for coronary events 1.25, CI 0.82–1.88, for HF 1.07, CI 0.71–1.62, for arrhythmias 0.82, CI 0.40–1.37, and for syncope 0.58, CI 0.13–2.71).

CONCLUSIONS
Although OH seems to be a predictor of coronary, cerebrovascular, and HF events, no predictive role was found in models that include biological confounders. Independent of the cause of OH, age and systolic BP, which are positively associated with OH, fully explain the greater incidence of cardiovascular events and the greater cardiovascular risk observed in subjects with OH.

Keywords: blood pressure; community; epidemiology; hypertension; population; risk.

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Orthostatic hypotension (OH), which sometimes leads to dizziness or syncope,1,2,3 is often observed in the elderly4,5 (both normotensive and hypertensive6), deriving from adrenoceptor dysfunction,7,8 low cardiac output,9 concomitant diabetes,10 and antihypertensive treatment.11,12 Although OH is considered a common, serious, and underrecognized problem13 and an independent risk factor for mortality and cardiovascular disease,3 it is very prevalent (5%–58%),14,15 and, at a population level, evidence supporting its role as a risk factor is very sparse.16–21 Some studies that show a putative prognostic role of OH are biased by flawed methodology,22 based on selected patients,23–26 merely retrospective,27 or indicate a prognostic effect of OH only or mainly in unadjusted analysis that is uncontrolled for confounders.28–30 Adjusting for confounders often abolishes any presumptive role of OH as a risk factor.29,30 In a metaanalysis based on 11 studies, the OH that resulted was devoid of any negative prognostic effect.31 The fear of inducing OH limits physicians who tend to undertreat hypertensive patients, leading to inadequate control of arterial hypertension (>30% of cases of syncope32 and many cases of falls33 are attributed to OH). Worldwide, arterial hypertension is undertreated, with normalization achieved in 6%–25% of cases.34 Physicians use excess caution due to a fear of being too aggressive and, in turn, causing hypotension (particularly OH). In addition, limited knowledge of current guidelines contributes to disappointing treatment results.35 While it has been proven that high blood pressure (BP) is followed by higher mortality and morbidity, a negative prognostic role of OH has yet to be demonstrated.

In our study we aimed to determine whether OH is associated with higher cardiovascular events or higher...
cardiovascular risk in a large, representative group of elderly men and women who were recruited in the frame of a population-based study.

**METHODS**

**Study population**

All white subjects aged ≥65 years living in 2 Italian towns were invited by letter to a screening in the frame of the Last Evidences Of Genetic Risk factors in the Aged (LEOGRA) study, a longitudinal epidemiological project described elsewhere. The subjects were followed by a staff of specialists for 12 years (from 2000 to 2012) or until death. As commonly observed in population-based studies organized in northern Italy, 73% of subjects adhered to the protocol and gave informed consent. No general characteristic differences were detectable between those who agreed to participate and those who were renitent (data not shown). No drop out was observed during follow-up.

The investigation conformed with the principles outlined in the Declaration of Helsinki and with institutional guidelines and was approved by the ethics committees of the University of Padova and Local Health Unit 4 of the Veneto region (Italy). Each subject gave and signed informed consent.

**Clinical evaluation and definitions**

At baseline and at each follow-up visit, all subjects were invited to receive a physical examination and complete a Rose’s questionnaire about medical history and smoking and drinking habits. BP was measured in triplicate using a validated oscillometric device (Omron 705 IT, Omron Europe, Hoofddorp, the Netherlands), with the appropriate cuff size and with the participants in the supine position after 10 minutes of bed rest. The average of the last 2 measurements was taken into account for data analysis. BP was also recorded immediately upon standing and after 1 and 3 minutes standing.

Subjects were labeled as having OH if they showed a decrease in systolic BP of at least 20 mm Hg or a decrease in diastolic BP of at least 10 mm Hg or both within 3 minutes of standing. These cutoff values are universally accepted and are valid for Italian subjects. Body mass index was estimated as body weight (in kilograms) divided by height in square meters. Serum blood glucose, serum total cholesterol, and low-density lipoprotein fraction serum triglycerides and serum uric acid were measured after fasting by automated methods.

Diabetic subjects were identified according to current American Diabetes Association guidelines or on the basis of current antidiabetic treatment confirmed by a general practitioner. In nondiabetic subjects, blood glucose was measured 1 hour after a 75-gm oral glucose load to determine serum peak glucose and serum insulin. The homeostasis model assessment index (HOMA-IR) was calculated (in arbitrary units) as follows: (circulating insulin (µU/mL) × fasting blood glucose (mmol/L))/22.5.

All subjects underwent a 2-dimensional guided M-mode echocardiogram with a device (Megas GPX device; Esaote, Firenze, Italia). The device had been validated and used in many studies by the same staff, and all the echocardiograms were taken by the same operator (E.G.). Left ventricular end-diastolic diameter, end-diastolic interventricular septum, and left ventricular posterior wall thickness were measured according to the American Society of Echocardiography and Penn convention. Recordings were analyzed automatically during the exam using the inner software and then analyzed off-line by an independent operator who did not know the study’s aim and design. A preliminary Bland–Altman analysis demonstrated very good agreement between the 2 measurements (data not shown), so that the average of the 2 measurements was used for data analysis. Left ventricular mass (in grams) was calculated as follows: 0.832 × [(end diastolic diameter + end diastolic septum + posterior wall thickness) – (end diastolic diameter)3] + 0.6] and indexed for body surface area (in square meters) calculated as follows: 71.84 × weight (kg)0.425 × height0.725. Men with left ventricular mass index >125 g/m2 and women >110 g/m2 were considered as having left ventricular hypertrophy.

Pulse wave analysis was performed by applanation tonometry. The radial arterial waveform was taken at the dominant arm 1 cm proximal of the bifurcation into the profound and superficial branches, and the carotid arterial waveform was taken at the common carotid 2 cm proximal of the bulb using a high-fidelity micromanometer (SPC-301; Millar Instruments Inc., Houston, TX) interfaced with a laptop computer running the SphygmoCor software 7.1 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). This software calculates the aortic pulse wave by means of a validated generalized transfer function and returns the central systolic BP and the pressure at the first and second peak or shoulder of the central and peripheral waveforms. Carotid–femoral transit time was estimated in 8 to 10 sequential electrocardiogram-gated femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. Carotid–femoral pulse wave velocity was calculated (in meters per second) as the carotid–femoral path length divided by the carotid–femoral mean transit time.

**Dietary questionnaire**

A 138-item food-frequency questionnaire was administered at the initial screening. The questionnaire was validated for the Mediterranean diet and has been used in previous studies by the same research group. The reported frequencies of food intake per week were converted to number of intakes per day and multiplied by the weight of the portion size indicated. The mass of each dietary item was calculated. Each food item was then broken down into its chemical components according to composition tables created specifically for Italian food; data were expressed as percent of food actually consumed after eliminating the scrap. Daily alcohol intake was calculated in grams ethanol based on a detailed questionnaire that asked for daily consumption of wine (ethanol 10%–12%), beer (ethanol 3%–7%), aperitifs...
(16%–24%), and spirits (ethanol 33%–46%). Daily caffeine intake was calculated based on the number of cups of coffee and tea per day after ascertaining experimentally that 1 cup of espresso Italian coffee contains 80 mg of caffeine. Dietary fiber intake was calculated as previously described.

Assessment of events

Vital status and events, including causes of death, were obtained from the Italian Register’s Office, and the incidence of fatal diseases was double-checked for causes of death by referring to hospitals, retirement homes, and physicians’ files. The incidence of nonfatal events was obtained via follow-up visits with repeated administration of the same standardized questionnaire used at baseline, via consultation with physician and retirement home records, and through DRG codes. All events from each participant were coded by a trained abstractor according to the International Classification of Diseases, 9th revision (ICD-9).

Cerebrovascular events, including ischemic and hemorrhagic stroke and transient ischemic attack, were described at baseline and at follow-up using ICD-9 codes 430–435, integrated when necessary by clinical history or positive computer tomography or positive magnetic resonance imaging. Coronary heart disease (CHD) was described using ICD-9 codes 410–414, integrated when necessary by clinical history or positive stress test, coronary angiography, or positive myocardial scintigraphy. Heart failure (HF) was described using ICD-9 codes 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, or 428.00–428.99, integrated when necessary by chest x-ray, echocardiogram, or circulating levels of N-terminal pro-B–type natriuretic peptide. Arrhythmic events, including atrial flutter and fibrillation, ventricular flutter and fibrillation, and paroxysmal supraventricular and ventricular tachycardia, were described using ICD-9 codes 4270–4279, integrated when necessary by basal or dynamic electrocardiogram. Syncope, including neurocirculatory ashenia, carotid sinus syncope, orthostatic hypotension, and vasovagal attack, was described using ICD-9 codes 3062, 3370, 4580, or 7802.

Statistical analysis

SAS software version 9.3 (SAS Institute, Cary, NC) was used. A priori power analysis based on previous experience indicated that 714 participants in equality for 2 proportions test were sufficient to show effects, if any, avoiding beta error with a power of 0.95 and a test level of 0.05. Linearity assumption was ascertained for each variable by the residuals method and normality assumption was ascertained by the Kolmogorov–Smirnov 1-sample test. Continuous variables were expressed as mean and standard deviation. After log transformation, analysis of variance was used to compare grouped continuous variables; the χ² test was used to compare the prevalence of categorical variables; and the log rank of Wilcoxon signed rank test was used to compare stroke-free survival between groups. Kaplan–Meier analysis was performed to compare event-free survival in groups of subjects. The null hypothesis was rejected when the P value was <0.05. Forward logistic analysis was used to determine whether OH was determined by independent variables. Cox proportional hazard models were used to find the variables with a prognostic role in incidence of events (<0.10 to enter and remove) and to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs).

RESULTS

Descriptive statistics

The general characteristics of the 1,016 subjects representing the elderly population of whom 419 (41.2%) were men are shown in Table 1 (see Supplementary Table S1 for more detailed information). OH was present in 168 subjects (60 men and 108 women). Its prevalence progressively increased with increasing age, both in men and women (Figure 1). Subjects with OH were significantly older, had higher prevalence of female gender, and had higher systolic BP values compared with those without OH.

In forward logistic regression analysis, age (odds ratio (OR), 0.96; P < 0.005), systolic BP (OR, 0.98; P < 0.001), body mass index (OR, 1.06; P < 0.005), and the orthostatic increment of plasma aldosterone (OR, 0.97; P < 0.03) were significant determinants of OH, while all other items that were checked, including pulse wave velocity, were rejected from the model.

Analysis of events

In the overall study population, median follow-up was 9.3 years (interquartile range, 7–10.6). During 8,503 person-years of follow-up, there were 522 documented fatal and nonfatal cardiovascular events: cerebrovascular in 93 cases, CHD in 145, HF in 151, arrhythmias in 118, and syncope in 15, with a median time to event of 8.2 years. A total of 237 cardiovascular events occurred in men during 3,387 person-years of follow-up (age-adjusted incidence rate 68.1 per 1,000 person-years) and 285 occurred in women during...
5,116 person-years of follow-up (age-adjusted incidence rate 52.9 per 1,000 person-years). Crude incidence rates of cardiovascular events were 67.7 per 1,000 person-years among participants with OH and 52.8 per 1,000 person-years among those without OH. Crude incidence rates of each cardiovascular event by OH status are summarized in Table 2 and by gender in Table 3.

When crude analysis irrespective of confounders was performed in the whole population, the incidence of events due to CHD, stroke, and HF was apparently greater in subjects with OH compared with those without OH, while no difference was detected for arrhythmias and syncope (Table 2).

The Kaplan–Meier curves are shown in Figure 2.

The HRs for CHD, stroke, and HF obtained from the unadjusted Cox model were also apparently significantly higher in subjects with OH (Table 4). Nevertheless, when the models were adjusted for age, gender, and systolic BP in the whole population, any cardiovascular events were no longer predicted by OH (Table 4). Age alone and systolic BP alone, but not gender alone, deprived OH of any predictive role (data not shown). Antihypertensive treatment as a categorical covariable did not modify the prognostic models significantly (data not shown).

A significant interaction was detected for OH with age for CHD (HR, 1.01; CI, 1.001–1.013; P = 0.01), stroke (HR, 1.003; CI, 1.001–1.013; P = 0.02), and HF (HR, 1.006; CI, 1.001–1.012; P = 0.02). Also, an interaction was detected for OH with gender for stroke (HR, 2.41; CI, 1.28–4.54; P < 0.01) and HF (HR, 1.98; CI, 1.16–3.39; P < 0.01) and with systolic BP for CHD (HR, 1.09; CI, 1.01–1.18; P = 0.02), stroke (HR, 1.09; CI, 1.00–1.20; P = 0.005), and HF (HR, 1.08; CI, 1.00–1.017; P = 0.04). In sensitivity analysis, stratification of the models by tertiles of age and tertiles of systolic BP (Supplementary Table S2) or use of median systolic BP (Supplementary Table S3) instead of the continuous variables did not alter the results variable significantly. Furthermore, use of HOMA-IR instead of diabetes or use of proteic + lipidic + glucidic intake instead of caloric intake did not alter the models (data not shown).

Stroke was significantly predicted by age (HR, 1.11; CI, 1.10–1.16; P < 0.001), diabetes (HR, 1.86; CI, 1.21–2.86; P < 0.005), and cigarette consumption (HR, 1.05; CI, 1.01–1.11; P = 0.015). CHD and HF were only predicted by age (HR, 1.09; CI, 1.06–1.12; P < 0.001 and HR, 1.12; CI, 1.10–1.15; P < 0.0001, respectively). OH was constantly rejected from the models.
DISCUSSION

Is OH a cardiovascular risk factor? There is no clear answer to this question because available data are limited. The only data based on the general population come from the city of Malmö\textsuperscript{15–17} as well as the Malmo Preventive Project (MPP) study. This study provided 3 analyses that led to the conclusion that OH acts as a cardiovascular risk factor. The studies were performed in 17%, 6%, and 4% of the whole population\textsuperscript{15–17}

The Atherosclerosis Risk in Communities (ARIC) study, which was limited to subjects aged 45–64 years, also found OH to be a risk factor.\textsuperscript{18} In that study, BP was taken in 30-second intervals for 2 minutes both in lying and standing postures, possibly leading to underestimation of the prevalence of OH. Other studies have been based on biased records\textsuperscript{22} or on selected patients\textsuperscript{23–26} or are retrospective;\textsuperscript{27} therefore, their results cannot be extended to the general population.

To our knowledge, this is the first study to take into account the entire elderly component of the general population living in a homogenous geographic area. The results shown here demonstrate that OH is not a cardiovascular risk factor and does not favor cardiovascular events when the analysis is conducted in unselected elderly men and women from the general population and when biological confounders are taken into account. In fact, although subjects with OH seemed to show an increased cardiovascular risk based on univariate analysis, any prognostic effects of OH were not present when age or systolic BP or both were included in the model. In other words, the apparent negative effect of OH

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Table 2. Crude incidence rate of cardiovascular events by orthostatic hypotension status in 1,016 elderly subjects

| Event               | Without OH (n = 848) | With OH (n = 168) | Statistics without vs. with OH |
|---------------------|----------------------|-------------------|--------------------------------|
|                     | Cases (n, %)         | Person-years      | Rate/1,000 person-years        |
| Stroke              | 71 (8.4)             | 6,918             | 10.3                           |
| Coronary heart disease | 111 (13.1)          | 6,827             | 16.3                           |
| Heart failure       | 117 (13.8)           | 6,747             | 17.3                           |
| Arrhythmias         | 99 (11.7)            | 6,752             | 14.7                           |
| Syncope             | 13 (1.5)             | 7,029             | 1.8                            |

| Event               | With OH (n = 168) | Person-years      | Rate/1,000 person-years        |                  |                  |
|---------------------|-------------------|-------------------|--------------------------------|------------------|------------------|
| Coronary heart disease | 34 (20.2)          | 1,329             | 25.6                           | \(\chi^2 = 10.4\) | \(P = 0.006\)    |
| Heart failure       | 34 (20.2)          | 1,331             | 25.5                           | \(\chi^2 = 5.86\) | \(P = 0.02\)    |
| Arrhythmias         | 19 (11.3)          | 1,346             | 14.1                           | \(\chi^2 = 4.60\) | \(P = 0.03\)    |
| Syncope             | 2 (1.2)            | 1,407             | 1.4                            | \(\chi^2 = 0.02\) | \(P = 0.91\)    |

Statistics without vs. with OH:

- \(\chi^2 = 3.76\), \(P = 0.05\)
- \(\chi^2 = 5.86\), \(P = 0.02\)
- \(\chi^2 = 4.60\), \(P = 0.03\)
- \(\chi^2 = 0.02\), \(P = 0.91\)

Abbreviation: OH, orthostatic hypotension.

Table 3. Crude incidence rate of cardiovascular events by gender in 1,016 elderly subjects

| Event               | Men (n = 419) | Person-years | Rate/1,000 person-years | Women (n = 597) | Person-years | Rate/1,000 person-years |
|---------------------|---------------|--------------|-------------------------|-----------------|--------------|-------------------------|
| Stroke              | 40 (9.5)      | 3,300        | 12.1                    | 53 (8.9)        | 4,985        | 10.6                    |
| Coronary heart disease | 66 (15.8)     | 3,198        | 20.6                    | 79 (13.2)       | 4,960        | 15.9                    |
| Heart failure       | 69 (13.8)     | 3,151        | 21.9                    | 82 (13.7)       | 4,926        | 16.6                    |
| Arrhythmias         | 59 (16.5)     | 3,161        | 18.7                    | 59 (9.9)        | 4,937        | 11.9                    |
| Syncope             | 3 (0.7)       | 3,371        | 0.89                    | 12 (2.0)        | 5,065        | 2.37                    |


was entirely explained by the confounders, being completely abolished after adjustment. Subjects with OH were older and had significantly higher systolic BP, 2 prognostic factors that fully explain the higher incidence of coronary and cerebrovascular events and HF, without any need to involve OH in the model.

These findings are in partial disagreement with the MPP and ARIC studies and with the study by Benvenuto et al., which showed an increased incidence of HF, coronary and cerebrovascular events, and atrial fibrillation in subjects with OH. On the other hand, these findings are in agreement with other data that showed no effect of OH on cardiovascular mortality in 2 large metaanalyses or after adjustment for confounders (particularly age and gender). In a recent metaanalysis, Xin et al. failed to find a significant association between OH and risk of cardiovascular-related death; the association between OH and all-cause mortality was largely attenuated when adequately adjusted by the classic risk factor. Our research group found the same evidence with another presumptive risk factor, menopause in women. In that case, acting at a population level, we demonstrated that, contrary to general belief, menopausal status is not a predictor of cardiovascular events once the models are adjusted for confounders.

Similar to menopause, OH seems not to be a risk factor in multivariate analysis of data from the general population. This evidence has important consequence in clinical practice. In fact, if OH is not a definite predictor of cardiovascular events and does not predispose to syncope, physicians should be encouraged to treat their hypertensive patients more aggressively, possibly leading to better control of BP. The fear of causing OH is one reason physicians are too cautious irrespective of guidelines, an approach that strongly contributes to the disappointing results of antihypertensive treatment.

### Table 4. Hazard ratio of orthostatic hypotension among the 1,016 elderly subjects

| Event                  | Hazard ratio     | P value |
|------------------------|------------------|---------|
| **Univariate unadjusted analysis** |                  |         |
| Stroke                 | 1.60 (CI 1.00–2.58) | 0.05    |
| CHD                    | 1.58 (CI 1.09–2.30) | 0.02    |
| Heart failure          | 1.49 (CI 1.03–2.17) | 0.04    |
| Arrhythmias            | 0.99 (CI 0.60–1.61) | 0.9     |
| Syncope                | 0.78 (CI 0.17–3.48) | 0.7     |
| **Multivariate analysis adjusted for age, gender, and systolic blood pressure** |                  |         |
| Stroke                 | 1.33 (CI 0.78–2.22) | 0.3     |
| CHD                    | 1.25 (CI 0.82–1.88) | 0.3     |
| Heart failure          | 1.07 (CI 0.71–1.62) | 0.7     |
| Arrhythmias            | 0.82 (CI 0.49–1.37) | 0.4     |
| Syncope                | 0.58 (CI 0.13–2.71) | 0.5     |

Abbreviations: CHD, coronary heart disease; CI, 95% confidence interval.
The strengths of our study are that it was population based, unbiased, prospective, and long lasting and it controlled for a great number of confounders without the need for multiple imputations. The limitation of the study is that the number of events among subjects showing OH was relatively small for arrhythmic events and syncope. Consequently, the results for these outcomes should be interpreted with caution.

In conclusion, based on our experience with a general population, OH is not a cardiovascular predictor for cerebrovascular, coronary, and arrhythmic events; HF; and HFpEF. The association of postural changes in systolic blood pressure and mortality in persons with hypertension: the hypertension detection and follow-up program experience. Circulation 1987; 75:340–346. Baragou S, Pio M, Pessina A, Redah D. Prevalence of orthostatic hypotension and its risk factors in treated hypertensive black Africans. Pan Afr Med J 2012; 11:12 (http://www.panafrican-med-journal.com/content/article/11/12/full/).

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