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The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study

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Abstract

Objective: to determine the prevalence of orthostatic hypotension (OH) and associations with medication use in community-dwelling older women.
Design: cross-sectional analysis using data from the British Women's Heart and Health Study.
Setting: general practices in 23 towns in the UK.
Participants: 3,775 women aged 60–80 years from 1999 to 2001.
Main outcome measure: orthostatic hypotension—drop of ≥20 mmHg in systolic and/or a drop of ≥10 mmHg in diastolic blood pressure on standing.
Results: prevalence of OH was 28% (95% confidence interval [CI] 26.6, 29.4), which increased with age and hypertension. Regardless of treatment status or diagnosed hypertension, raised blood pressure was strongly associated with OH ($P < 0.001$). OH was strongly associated with number of antihypertensives taken (none vs three or more: odds ratio [OR] 2.24, 95% CI 1.47–3.40, $P < 0.001$); the association was slightly attenuated after allowing for age and co-morbidities (OR 1.99; 95% CI 1.30, 3.05; $P = 0.003$). Women with multiple co-morbidities had markedly increased odds of OH independent of age, number and type of medications taken (none vs four or more diagnoses: OR 2.28, 95% CI 1.58–3.30, $P = 0.005$).
Conclusion: uncontrolled hypertension, use of three or more antihypertensives and multiple co-morbidities are predictors of OH in older women. Detection or monitoring of OH in these groups may prevent women from suffering its adverse consequences.

Keywords: *orthostatic hypotension*, *prevalence*, *medication*, *elderly*

Introduction

Compensatory mechanisms are required in order to regulate blood pressure in old age. Baroreflexes, which control heart rate and vascular resistance, decline in efficiency with ageing, resulting in a tendency for systolic blood pressure and pulse pressure to fall upon standing [1, 2]. A reduction in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg within 3 min of standing is defined as orthostatic hypotension (OH) [3].

The reported prevalence of OH varies between 5% in community residents and 60% in people in institutions and acute-care settings [4]. OH is more prevalent in elderly people [2, 5], diabetic [6, 7] and hypertensive individuals [5–9]. An increased risk of falls [10], cerebrovascular events [6, 11] and mortality [2, 8, 12] have been reported in patients with OH.

Medications have been implicated in the development of OH, in particular anti-hypertensive agents [4, 10]. Polypharmacy refers to the prescription of more drugs than is clinically justified [13], and this occurs frequently in older adults. Presentation to the emergency department is more likely the greater the number of medications used and the older the patient [14], and a fall due to OH may be the precipitating factor. We examined the association between OH

and patterns of medication use in community-dwelling older women.

Methods

The British Women's Heart and Health Study (BWHHS) methodology has been fully described elsewhere [15]. Briefly, between 1999 and 2001, a cohort of 4,286 women was recruited from general practice lists in 23 nationally representative UK towns. Participants attended an interview where they were asked about diagnosed diseases, and were also asked to bring in all their current medications so that these could be recorded. Women completed a questionnaire collecting behavioural and lifestyle data, including smoking habit, alcohol consumption and indicators of socio-economic position. Their blood pressure levels were measured at the time of the interview, with two sitting measurements followed by two standing measurements (all at 1-min intervals). OH was defined as a drop of ≥10 mmHg in diastolic blood pressure and/or a drop of ≥20 mmHg in systolic blood pressure on standing (based on the differences between the first sitting and fourth standing measurements, within 3 min of standing). These measurements were taken in the morning for all patients who were also fasting. Participants were advised to take any regular medications on the day of examination.

Disease status was assessed by interview at baseline, self-completed questionnaire and by general practitioner record review. A diagnosis of coronary heart disease (CHD), stroke or diabetes was accepted using any of these methods. 'Evidence of hypertension' included women identified as hypertensive from self-reported doctor diagnosis of hypertension (regardless of blood pressure at medical examination) plus those without a self-reported diagnosis who had high blood pressure at medical exam. High blood pressure (BP) was defined as a systolic pressure of >140 mmHg and/or diastolic pressure of >90 mmHg according to British Hypertension Guidelines [16] as well as other international bodies [17, 18]. In addition, three groups were differentiated: 'controlled hypertensives', that is, known hypertension (self report) with normal blood pressure ≤140/90 mmHg on antihypertensive medication; 'uncontrolled hypertensives', that is, elevated BP (>140 mmHg systolic pressure and/or >90 mmHg diastolic pressure) and on antihypertensive medication; and 'normotensives'. Circulatory disease was defined as any diagnosis of myocardial infarction, angina, stroke, transient ischaemic attack, aortic artery disease or peripheral artery disease. Chronic obstructive pulmonary disease (COPD) included asthma and chronic bronchitis, and eye disease included cataracts and glaucoma [15]. Diabetes was defined using the World Health Organization criteria [19] of a fasting blood glucose ≥7 mmol/L or report of a diagnosis of diabetes.

Analyses were confined to 3,775 women (88% of total women) who had blood pressure measurements made at examination and with information on medications (both prescribed and bought over the counter) collected at interview by a trained nurse. Characteristics of women, including disease status and medications taken, were compared according to presence or absence of OH. Odds ratios (OR) of OH were calculated for the different medications grouped according to class of drug using the British National Formulary categories [20] adjusted for age alone, for other medications and additionally for disease and lifestyle variables. These were calculated using conditional logistic regression analyses, adjusted for town of residence to account for the clustered sampling strategy used in recruitment.

This study has approval from the 23 local research ethics committees covering our study population. All women gave signed informed consent at baseline.

Table 1. Characteristics of women with or without OH. Values are percentages of women (number of women) by risk factors, disease status and medications taken

	Without orthostatic hypotension (n=2,716)	With orthostatic hypotension (n=1,059)	P value adjusted for age[a]
Risk factors:			
Age: mean (SD)	68.4 (5.4)	69.4 (5.5)	
Body mass index: mean (SD)	27.6 (4.8)	27.2 (4.8)	0.06
Alcohol (over 14 units per week), %	5.9 (161)	4.1 (43)	0.03
Manual social class, %	53.4 (1,452)	53.4 (566)	0.79
Current smoker, %	11.4 (311)	9.4 (100)	0.14
Disease status, %:			
Evidence of hypertension[b]	64.1 (1,740)	79.2 (839)	<0.001
Arthritis	46.5 (1,264)	44.9 (476)	0.36
Any circulatory disease	25.6 (695)	26.1 (276)	0.57
Chronic obstructive lung disease	22.3 (606)	22.9 (243)	0.35
Depression	15.4 (419)	15.7 (166)	0.47
Coronary heart disease	15.6 (424)	16.0 (170)	0.69
Eye disease	13.6 (370)	14.9 (148)	0.85
Thyroid disease	10.3 (281)	10.9 (115)	0.76
Diabetes	8.8 (239)	10.9 (115)	0.14
Cancer	8.7 (236)	9.0 (95)	0.82
Medication, %:			
On any BP-lowering medication	33.8 (919)	40.2 (426)	<0.001
Beta blockers	12.8 (347)	18.2 (193)	<0.001
Thiazide diuretic	12.9 (351)	16.2 (172)	0.008
Calcium channel blockers	10.7 (291)	10.9 (115)	0.90
Angiotensin-converting enzyme inhibitors	8.8 (238)	11.0 (116)	0.04
Non-thiazide diuretic	8.5 (231)	9.7 (103)	0.25
Nitrates	7.8 (213)	6.6 (70)	0.20
Alpha-adrenoceptor-blocking drugs	1.4 (37)	2.5 (26)	0.02
Central nervous system	28.5 (773)	26.1 (276)	0.14
Endocrine system	21.3 (579)	22.6 (239)	0.40
Antiplatelet drugs	13.5 (367)	14.5 (154)	0.40
Respiratory system	11.2 (305)	12.6 (133)	0.20
Lipid-lowering drugs	7.9 (215)	8.6 (91)	0.50
Any other drug	31.2 (848)	30.8 (326)	0.80

[a]P values are derived from conditional logistic regression of OH on age and each specified variable in turn.

[b]Comprises of doctor diagnosis of hypertension and those without doctor diagnosis who had high blood pressure readings at baseline medical examination (>140 mmHg systolic and/or >90 mmHg diastolic pressure).

Table 2. Relationship between type of drug used and OH in 3,749 UK women[a] aged 60–80 years. Values are adjusted odds ratio of OH (95% CI)

	Adjusted for age	Adjusted for age and for other drugs listed	Additionally adjusted for disease and lifestyle variables[b]
On any BP-lowering medication	1.26** (1.09, 1.47)	0.95 (0.70, 1.30)	0.80 (0.58, 1.10)
Beta blockers	1.47*** (1.23, 1.81)	1.59** (1.21, 2.10)	1.58** (1.19, 2.09)
Thiazide diuretic	1.25* (1.02, 1.53)	1.18 (0.90, 1.55)	1.16 (0.88, 1.52)
Calcium channel blockers	0.96 (0.76, 1.21)	0.95 (0.72, 1.27)	0.95 (0.71, 1.27)
Angiotensin-converting enzyme inhibitors	1.27* (1.00, 1.61)	1.26 (0.94, 1.69)	1.23 (0.92, 1.66)
Non-thiazide diuretic	1.07 (0.83, 1.37)	1.09 (0.84, 1.43)	1.13 (0.86, 1.49)
Nitrates	0.77 (0.58, 1.02)	0.70* (0.51, 0.96)	0.72 (0.49, 1.05)
Alpha-adrenoceptor-blocking drugs	1.81* (1.08, 3.03)	1.59 (0.92, 2.72)	1.51 (0.88, 2.58)
Drugs for central nervous system	0.86 (0.73, 1.02)	0.86 (0.72, 1.01)	0.86 (0.72, 1.03)
Drugs for endocrine system	1.14 (0.96, 1.35)	1.12 (0.94, 1.33)	1.13 (0.92, 1.38)
Drugs for respiratory system	1.14 (0.91, 1.42)	1.24 (0.99, 1.56)	1.21 (0.93, 1.56)
Antiplatelet drugs	0.96 (0.78, 1.19)	0.90 (0.71, 1.14)	0.88 (0.68, 1.13)
Lipid-lowering drugs	1.10 (0.85, 1.43)	1.05 (0.79, 1.41)	1.00 (0.74, 1.34)
Any other drugs	0.94 (0.81, 1.10)	0.94 (0.79, 1.11)	0.93 (0.78, 1.11)

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
[a]Restricted to 3,749 women with medication, OH, disease and lifestyle variables available.
[b]Disease and lifestyle variables adjusted for: high blood pressure, any circulatory disease, CHD (myocardial infarction or angina), diabetes, cancer, COPD, arthritis, thyroid disease, eye disease, depression, heavy alcohol drinker (daily or ≥14units/week), social class and smoking status.

Results

The characteristics of women with and without OH are shown in Table 1. There was a higher prevalence of OH amongst women who had evidence of hypertension (79% vs 64%, $P < 0.001$), but no associations were seen with coronary heart disease, circulatory disease, diabetes, chronic obstructive pulmonary disease, cancers and other chronic diseases.

The prevalence of OH was 28% (95% confidence intervals [CI] 26.6, 29.4) amongst our women aged 60–80 years. Systolic OH was more frequent than diastolic OH (20.4% vs 12.4%). This prevalence varied substantially by age and by presence of diagnosed hypertension, from 21% amongst women aged 60–64 without hypertension to 32% amongst women aged 75–80 with hypertension. See the table Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/. The effects of blood pressure on the odds of OH do not differ by age group (P for interaction = 0.32). Overall, the prevalence of OH was 24% higher in women who reported a diagnosis of hypertension. The prevalence of OH in this diagnosed hypertension group was fairly similar between those who received blood-pressure-lowering treatment and those who did not (33% vs 29%). However, in the treatment group, OH was significantly higher among the 'uncontrolled' hypertensives (38% vs 21%, P value for difference <0.001). Among women who reported no diagnosis of hypertension, OH was nearly twice as prevalent (33% 95% CI 30.6, 36.1 vs 18% 95% CI 16.2, 20.6) in those who were categorised as 'undiagnosed hypertensives' compared to those who were 'normotensives' ($P < 0.001$).

Higher odds of OH were observed amongst women taking any blood-pressure-lowering medication (age-adjusted OR 1.26, 95% CI 1.09–1.47, $P < 0.01$). However, only evidence of associations between OH and beta blockers remained after adjustment for age, co-morbidity and health behaviours (OR 1.58; 95% CI 1.19, 2.09; $P < 0.01$; Table 2). There was evidence that taking nitrates reduced the odds of OH after adjusting for age and other drugs (OR 0.70; 95% CI 0.51, 0.96; $P < 0.05$). This association, however, was attenuated after adjusting for diseases and lifestyle variables ($P = 0.08$).

The odds of OH did not increase with the overall number of drugs being taken. See the table Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/. However, the odds of OH did increase in those on multiple antihypertensive drugs (none vs three or more: crude OR 2.24, 95% CI 1.47–3.40, $P < 0.001$). This association was modestly attenuated by adjustment for age (OR 2.09, 95% CI 1.37–3.18, $P < 0.001$) and number of diseases (OR 1.99, 95% CI 1.30–3.05, $P = 0.003$). To determine whether the number of drugs or the number of co-morbid diseases was the more important factor, an analysis of odds ratios for OH by number of co-morbidities was carried out (Table 3). In age-adjusted analyses, women with an increasing number of diseases (from none up to four or more diseases) had increased odds of having OH (OR 2.40; 95% CI 1.70, 3.38; $P = 0.007$). This association remained when adjusted for both age and number of drugs taken (OR 2.28, 95% CI 1.58–3.30, $P = 0.005$). We also examined potential adverse outcomes associated with OH. OH was not significantly associated with falls (age-adjusted OR 0.96; 95% CI 0.79,

Table 3. Relationship between number of diseases and OH. Values are crude and adjusted OR of OH (95% CI)

Number of diseases[a]	Odds ratios (95% CI)				
	% with OH	n=3,780	Crude	Adjusted for age	Adjusted for age and number of drugs
0	16.4	292	1.00	1.00	1.00
1	27.3	938	1.82 (1.19, 2.78)	1.68 (1.10, 2.58)	1.84 (1.31, 2.60)
2	28.5	1,005	2.09 (1.37, 3.18)	1.87 (1.22, 2.85)	1.95 (1.38, 2.74)
3	28.5	740	2.26 (1.47, 3.47)	1.94 (1.26, 3.00)	1.93 (1.35, 2.77)
≥4	32.0	805	3.03 (1.99, 4.62)	2.48 (1.62, 3.80)	2.28 (1.58, 3.30)
P value[b]	0.0001		<0.001	<0.001	0.005

[a]Number of diseases includes diabetes, any circulatory disease, coronary heart disease, high blood pressure, thyroid disease, eye disease, arthritis, cancer, depression and COPD.
[b]P value from Mann–Whitney U test for percent with OH; P value for trend for ORs from logistic regression analysis.

1.17; $P = 0.70$) or cerebrovascular events (age-adjusted OR 1.15; 95% CI 0.88, 1.50; $P = 0.30$). However, OH was strongly associated with all-cause mortality over the 7.6 years of follow-up since baseline blood pressure measurement (age-adjusted OR 1.10; 95% CI 1.07, 1.14; $P < 0.001$).

Discussion

The prevalence of OH in British women was high when compared to other community elderly study populations. Associations with increasing age [2, 5], hypertension [5, 7–9] and death [2, 8, 12] were confirmed. Use of beta blockers and three or more antihypertensives were independently associated with OH. Multiple co-morbidities and uncontrolled hypertension were also strong predictors of OH in older women. No association of OH with cerebrovascular events, diabetes or falls was found, failing to support earlier findings [6, 7, 10, 11].

The risk of OH was higher in women on antihypertensives, as shown in smaller studies [7, 10], and rose with the number of antihypertensive drugs taken. However, contrary to expectations, there was no evidence to suggest that polypharmacy was associated with OH. Given the increased emphasis on achieving blood pressure control through use of at least two antihypertensives, our findings indicate the need for clinicians to be cautious and provide close monitoring of symptoms and signs of OH when multiple agents are used in hypertensive older adults. In frail elderly people, efforts to achieve optimal therapeutic control should be balanced with consideration of their complex and multiple co-morbidities, which render them at greater risk of OH and its consequences. In contrast to other studies [5, 6, 21], OH was strongly associated with the number of co-morbidities but not with each individual co-morbidity. This was independent of the number of drugs taken. This may be partly explained by the higher number of co-morbid diseases in our older participants compared with those in other studies. This association may relate to pathophysiological changes such as peripheral sympathetic failure or atherosclerosis with diabetes [7] as well as other age-associated diseases that impair autonomic function [22].

OH is associated with hypertension-related alterations in blood pressure regulation. With increasing age and regardless of treatment status or doctor diagnosis of hypertension, we found that OH was strongly associated with high blood pressure at baseline, above the recommended guidelines for treatment [16–18]. This indicates that undetected high blood pressure, rather than antihypertensive drugs, is a sufficient cause of OH. The combination of hypertension and OH in older adults is becoming increasingly recognised but may be due to the association of both OH and high blood pressure with increasing age [21]. Older hypertensive patients often display lability in blood pressure possibly via altered sympathovagal balance, increased left ventricular wall thickness, decreased left ventricular preload and alterations of left ventricular diastolic filling [23]. Improvement in postural blood pressure changes may occur with prolonged treatment with certain antihypertensive medications, possibly related to their action on reducing left ventricular wall thickness and enhancement of stroke volume [9, 24]. However, owing to the cross-sectional design of the study, we were unable to determine whether this association was related to duration of treatment with the various antihypertensives or not.

The mechanism for drug-induced OH is related to interference with reflex responses by drugs that may limit vasoconstriction, heart rate or cardiac output adjustments or exaggerate venous pooling such as vasodilators, alpha- and beta-adrenergic blockers, calcium channel blockers (CCB) and nitrates [25]. OH occurs via volume depletion with diuretics. It has been suggested that it may be a misconception to attribute OH to any particular type of antihypertensive due to a relatively high prevalence of OH among elderly patients in general [26]. However, in keeping with other studies [7, 10], our study showed strong age-adjusted associations with OH in women taking beta blockers, alpha-adrenoceptor blockers, thiazide diuretics and angiotensin-converting enzyme (ACE) inhibitors. Despite its intrinsic sympathomimetic activity and the reported effects of longstanding beta-blocker treatment in protecting the elderly from OH [22], the stronger relationship between OH and beta blockers may be due to its use in women with (as yet undetected) underlying coronary artery disease and

left ventricular impairment. Expected associations with OH in those taking the older alpha-adrenoceptor blockers and CCBs [4, 7, 10] were not observed. This may reflect use of CCBs in patients suffering from coronary artery disease in addition to hypertension [20]. Despite having a more gradual onset of action and less postural hypotensive effects, women taking newer alpha-adrenoceptor blockers such as doxazosin still had a particularly strong age-adjusted odds of OH, although few were on these types of antihypertensive. Although nitrates have been associated with OH, especially in conjunction with other antihypertensives such as ACE inhibitors [20], there was modest evidence for a negative association with OH ($P = 0.03$). This 'protective effect' could be related to nitrate tolerance in those on sustained therapy [27]. There is evidence suggesting that some nitrates, particularly Glyceryl trinitrate (GTN), are associated with reduced bioavailability of GTN-derived nitrous oxide, impairing its vasodilator activity and, possibly, directly counteracting GTN-induced vasorelaxation [28].

Strengths and limitations

The BWHHS is a large, population-based cohort which is representative of British women. It has nurse-verified data on prescribed medications which reflect prescribing practices in a wide range of locations in the UK. We were also able to obtain blood pressure measurements according to a precise protocol applied by trained nurses, enabling us to measure OH objectively. Although our response rate (60%) is moderate, it is consistent with other large contemporary epidemiological surveys [29]. The respondents in our study were slightly younger than non-respondents, hence the results on the prevalence of OH in the general community may be an underestimation, especially since OH and medication use are generally more common in older age groups (>80 years) who were not part of our study. However, the prevalence we observed was considerably higher than that reported in earlier community studies [2, 12]. This higher prevalence may be due to a higher sitting systolic blood pressure taken at baseline. This 'elevated' first reading may be related to 'white coat hypertension' usually experienced when blood pressure is first taken upon consultation. Furthermore, the women were also told to take their medication before attending the medical examination and hence this too affected the prevalence of OH among them.

As this analysis is cross-sectional, we cannot examine the effects of changes in the prescribing of drugs, and it is possible, but unlikely, that the associations observed are susceptible to reverse causality. Also, the lack of relationship of OH with the use of one drug relative to another may reflect the play of chance, and the confidence intervals include the possibility of a modest increase in risk of OH. There were no available data on how many of these had symptomatic OH at the time of measurement. Post-prandial OH was not considered as all respondents were fasting at time of blood pressure measurements.

Implications

Although treatment of hypertension in older people is effective in cardiovascular disease prevention [30], OH or its symptoms are a major reason for withdrawal of antihypertensives. We recommend that judicious prescribing of specific classes of antihypertensives (i.e. beta blockers and use of three or more antihypertensives) is required if OH and its consequences are to be avoided. Checking for OH as part of routine detection and control of hypertension in primary care in view of the strong association of OH among those with previously unrecognised raised blood pressure would be a useful step in assessing the need for antihypertensive treatment.

Key points

- Multiple co-morbidities are a more powerful independent determinant of orthostatic hypertension than the overall number of drugs taken.
- Orthostatic hypotension is particularly common in women with previously unrecognised raised blood pressure, so checking for this as part of routine surveillance in primary care is necessary.
- Blood pressure lowering with beta blockers and the use of three or more antihypertensives are independently associated with orthostatic hypotension, regardless of co-morbidities, and therefore close monitoring of signs and symptoms of OH is needed.

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Contributors

All authors developed the study's aim and design and managed its data. All authors contributed to the final version. S.E. will act as guarantor for the paper.

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Conflicts of interest

None.

Ethical approval

Local ethics committees approved the study, and 99.4% of participants gave written informed consent for their medical records to be available.

Supplementary data

Supplementary data mentioned in the text is available to subscribers at the journal website http://ageing.oxforjournal.org

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