Orthostatic hypotension, carotid artery wall thickness and use of anti-hypertension medication in a community-based sample of middle-aged Finnish men.

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Abbreviation: 95% CL (95 percent confidence limits)

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Introduction

Orthostatic hypotension is a condition characterized by a significant drop in blood pressure upon standing. It is found in 6 to 30% of elderly populations (1,2,3,4,5,6,7) and is associated with falls (8) and all-cause mortality (9). Some cases of the disorder are due to known ailments, like Shy-Drager syndrome (10) and other neurological and functional conditions (11,12). However, the vast majority of orthostatic hypotension cases have an unknown cause. Theoretically, any disorder affecting peripheral resistance, or the neurohormonal, brain, or autonomic systems could be a cause of orthostatic hypotension (13).

MacCellen et al. (14) and other investigators (15) have suggested a role for "mechanical defects in the artery" in orthostatic hypotension. This functional defect, affecting peripheral resistance, could be due to a number of factors including atherosclerotic processes, hypertrophy of the smooth muscle cells of the vessel wall, or both. Processes which cause the walls of the artery to thicken lead to a decline in arterial distensibility, compliance, or elasticity. This decline in distensibility, ~~a well-known part of the aging process (16),~~ could attenuate the ability of vessels to rapidly respond to changes in posture.

These analyses examine the ~~role of~~ association between carotid wall thickening and anti-hypertensive medication use and orthostatic hypotension in a middle-aged population of Finnish men. The data ~~set used~~ came from the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), ~~allows for adjustment of~~ a comprehensive population-based study which allows examination of a number of plausible confounders of this ~~relationship~~ association.

Methods

Study population

The KIHD participants are composed of two randomly selected samples from the Kuopio region in Eastern Finland. Complete details concerning the study design are published elsewhere (17, 18). These analyses are based on cohort 2 which is an age-stratified sample of men 42, 48, 54, or 60. A total of 1,836 were eligible for the study and 1,516 (83 percent) participated. The subjects were examined between August 1986 and December 1989 on a date near their birthday. This analysis includes the 1,315 men ~~who~~ with complete information on supine and standing blood pressure measurements, ~~information on~~ antihypertensive medication status, and who also participated in ultrasound measurements of the carotid artery, which started in 1987.

Variables

Blood Pressure: Blood pressure readings were taken at five, ten, and fifteen minutes in the supine position by a trained technician using a Hawksley Random Zero device. The 10 and 15 minute readings were averaged for this analysis. After being in the supine position for 15 minutes the patients were asked to stand. One minute after attaining upright posture with the right arm relaxed and hanging by the respondent's side, standing blood pressure was measured. The first and fifth Korotkoff sounds were used to represent systolic and diastolic blood pressure respectively. Blood pressures were measured after the subject had emptied his bladder, and none of the subjects had had a meal in the previous two hours (19).

Orthostatic Hypotension: Postural changes in blood pressure were calculated as the difference between the standing and the average supine blood pressure (standing minus supine). Those with a drop of ≥ 20 mm Hg in systolic blood pressure or ≥ 10 mm Hg in diastolic blood pressure or who reported "feeling faint" upon standing were categorized as having orthostatic hypotension.

Pulse Pressure: Pulse pressure was calculated as the difference between supine systolic blood pressure and supine diastolic blood pressure. Because the blood pressure readings used for pulse pressure were the same as those used in defining orthostatic hypotension we were concerned with bias resulting from regression to the mean (20). Therefore, a second pulse pressure variable was created to counteract this potential problem. This variable, based upon the method described by Oldham (21), used the average of supine and standing systolic minus the average of supine and standing diastolic blood pressure as pulse pressure. We have termed this variable "Oldham's pulse pressure."

Intima-medial thickening of carotid artery: This was assessed by ultrasonography. The B-mode scanning protocol involved scanning of the right and left common carotid artery and the carotid bifurcation. The site of the most advanced atherosclerotic lesion and the projection showing the greatest distance between the lumen-intimal interface and the media-adventitia interface was located in the right and left common carotid arteries (22) and recorded as a continuous variable. The readings were then graded into four categories: no lesions, any intima-medial thickening, plaque, and stenosis. Any intima-medial thickening was defined as a distance of more than 1.2 mm between the lumen-intimal interface and the media-adventitia interface during the diastole of

the cardiac cycle. A lesion was defined as a "plaque" if a distinct area with more than 50% greater intimal plus medial thickness (usually > 2.0 mm) could be defined relative to neighboring areas. Finally, if the plaque obstructed more than 20% of the lumen diameter, the finding was categorized as stenosis. A validity study indicated excellent intra-observer agreement (23).

Medication: Antihypertensive medication may cause orthostatic hypotension itself (24). Conversely, the use of anti-hypertensive medication could be a marker for underlying diseases related to mechanical defects and other risk factors for orthostatic hypotension (25, 26). To get information on anti-hypertensive medications, the participants were asked to list in the questionnaire the brand names of all prescribed drugs they were currently taking. The examining physician reviewed this information with the participant. The medications were coded according to the Nordic Pharmacopoeia. Anti-hypertensive medication type was divided into beta-blockers, diuretics, and others.

Disease history: A questionnaire was administrated concerning prior diagnosis of disease. This self-reported information was confirmed in the medical history taken by the research physician at the baseline examination. For these analyses four dichotomous disease history variables were created: 1) History of hypertension, 2) History of diabetes, 3) History of cardiovascular diseases (including angina, myocardial infarction, claudication, congestive heart failure, cardiomyopathy, and varicose veins) and 4) History of at least one psychiatric or neurohormonal disorder (mild mental problems, epilepsy, hyperthyroidism).

Risk Factors: Body mass index was calculated by participant's weight in kilograms divided by height in meters squared. Smoking status was divided into three categories: current smoker (smoked in the last month), former smoker, and never smoker. The latter was considered the reference group in logistic models. Alcohol consumption was based on one-year recall of the average consumption per week using the Nordic Alcohol Consumption Inventory, which is a quantity frequency measure from the Scandinavian drinking survey (28). Four categories were formed based upon grams of alcohol per day: nondrinkers and approximate tertiles of drinkers: > 0.0 to 8.0 g/week, > 8.0 to 57 g/week, and > 57 g/week. In logistic models, non-drinkers were considered the reference group.

Statistical methods

All analyses were done using the Statistical Analysis System version 6.04 (29). Prevalence of orthostatic hypotension was calculated by age, carotid wall thickening category, and anti-hypertensive drug use. Exact ninety-five percent confidence intervals (95% CL) were determined for all prevalence estimates based upon the binomial distribution.

The linear trend of pulse pressure (and Oldham's pulse pressure) with age was evaluated in a simple linear regression model. Using logistic regression, odds ratios were calculated to determine the association between orthostatic hypotension, and carotid wall thickness categories and antihypertensive drug use. Six separate, mutually exclusive categories were formed based upon the three groups of carotid wall thickening combined with two levels of antihypertension medication use: 1) No lesions and not using antihypertensive drugs, 2) No lesions and using anti-hypertensive medication 3) Any thickening of the intimal-layer and not using anti-hypertensive medication 4) Any thickening of the intimal-layer and using anti-hypertensive medication, 5) Plaque or stenosis and not using anti-hypertensive medication and 6) Plaque or stenosis and using antihypertensive medication.

Six logistic regression models were fit to estimate the association between these different categories of carotid artery wall thickness and orthostatic hypotension. In each model, five dummy variables were used to represent categories 2 through 6. In all cases the reference group was those individuals who had no lesions and did not use anti-hypertensive medication

Model 1 was the crude odds ratios. Model 2 included only adjustment for age. In addition to age, Model 3 was adjusted for history of hypertension, Model 4 was adjusted for cardiovascular disease history, Model 5 was adjusted for diabetes history, Model 6 was adjusted for history of neurohormonal diseases, and Model 7 was adjusted for body mass index, alcohol consumption, and smoking. Models 3-7 were compared to the age-adjusted model (Model 1) using the log-likelihood ratio test (30). These models were fit assuming the log odds for orthostatic hypotension were a linear function of age. This assumption was tested in all models by entering age as three dummy variables (the reference group being the 42-year-old subjects). If the

coefficients for the carotid thickness variables were similar in both models, we reported the model which assumed linearity.

Attributable fraction (AF), the proportion of all cases attributable to the exposure category (i.e., carotid wall thickness and anti-hypertensive medication use), were calculated using the following formula (31):

This seems unnecessary - the reference should be sufficient.

(2) ?

$AF_i=[p_{OHi}(OR_i-1)]/OR_i$, where

OR_i=odds ratios in the ith exposure category

p_{OHi} =prevalence of orthostatic hypotension in the ith exposure category.

i = 2,3,4,5,6

The 95 percent confidence intervals for the attributable fractions were approximated assuming constant prevalence of orthostatic hypotension.

Results

There were 287 men who were 42 years of age (22 percent of the sample), 306 men who were 48 years of age (23 percent), 370 men who were 54 years of age (28 percent) and 352 men who were 60 years of age (27 percent).

The average (± standard deviation) for supine systolic and diastolic blood pressure was 133.4 mmHg (± 17.2) and 85.4 mmHg (± 10.5) respectively. The average (± standard deviation) for standing systolic and diastolic blood pressure was 131.8 mmHg (± 18.6) and 94.0 mmHg (± 11.9) respectively. The average (± standard deviation) postural change in systolic and diastolic blood pressure was -1.7 mmHg (± 11.2)and 8.5 mmHg (± 7.1).

The overall prevalence of orthostatic hypotension was (n=78) 5.9 percent (95 % CL: 4.8, 7.3). Those with a drop of ≥ 20 mm Hg in systolic blood pressure comprised 82.1 percent (64 of 78) of the cases, those with a ≥ 10 mm Hg drop in diastolic blood pressure were 6.4 percent (5 of 78), and the remaining 11.5 % (9 of 78) were classified on the basis of both systolic and diastolic blood pressure. No cases were ascertained by the report of "feeling faint" upon standing.

The prevalence of orthostatic hypotension rose with age: In those aged 42 years the prevalence was 1.7 percent (95 % CL: 0.7, 4.0), in 48-year-olds, 4.2 percent (95 % CL: 2.5, 7.1), in 54 year old men 6.8 (95 % CL: 4.6, 9.8) and 9.9 percent (95 % CL: 7.2, 13.5) in those aged 60 years (Figure 1).

Pulse pressure and Oldham's pulse pressure were both approximently normally distributed by visual examination and both had a positive increase with age (p<.001).

The pulse pressure was slightly higher among those with orthostatic hypotension (mean = standard deviation: 43.0 mmHg ± 14.0) than among those without orthostatic hypotension (41.6 mmHg ± 11.5), this relationship was not statistically significant (p=0.42). The results for the Oldham's pulse pressure were similar: among cases the mean (± standard deviation) was 42.9 mmHg (± 11.7) and among non-cases 42.0 mmHg (± 12.5) (p=0.74).

Of the 1,315 men, 619 (47 percent) had no lesions in the carotid wall, 273 (21 percent) had some thickening, 386 (29%) had plaque and 37 people (3 percent) had stenosis. For logistic modeling the cases with plaque and stenosis were combined. The prevalence of orthostatic hypotension increased with thickening of the carotid artery wall: Among those with no lesions, 3.1 percent (95 % CL: 2.0, 4.7) had orthostatic hypotension, in those with any thickening, 4.8 percent (95 % CL: 2.8, 8.0) and in those with plaque or stenosis 10.9 percent (95 % CL: 8.3, 14.2).

Sixteen percent of the men (n=218) were on antihypertensive medication. The prevalence of orthostatic hypotension was 4.1 percent (95 % CL: 3.1 , 5.2) among those not using anti-hypertension medication and 14.8 percent (95 % CL: 10.6, 20.0) among those using anti-hypertensive medication. Among those using diuretics, 25 percent (10 of 40) had orthostatic hypotension, while 14 percent (18 of 124) of beta-blocker users had the disorder.

The crude prevalence of orthostatic hypotension is listed in Table 1.

The crude odds ratios were significantly affected by adjustment for age (Table 2) and all subsequent models were compared to the age-adjusted model. Table 2 shows that the age-adjusted odds ratios were not significantly affected by the covariates included in models 3 through 7.

Table 3 shows the age-adjusted odds ratios with three different types of contrasts. Column 1 shows the joint effect of carotid wall thickening and anti-hypertensive drug use compared to the group with no lesions and not using anti-hypertensive drug use. Column 2 shows that among those taking anti-hypertensive medication taking medication there is not a statistically significant carodid wall thickening effect. The association between carotid wall thickening and orthostatic hypotension was about 1.4 to 1.6 times stronger among those using anti-hypertensive medication in all models.

Column 3 shows that within categories of carotid wall thickening, there is a statistically significant drug effect. — this needs to be spelled out. The reader will forget what you mean by "effect"

Based upon the age-adjusted odds ratios, attributable fractions were calculated for each category of carotid wall thickness. Attributable fractions can be interpreted as the maximum proportion of potential cases that would be prevented if the exposure were completely eliminated in the source/target population. Figure 2 summarizes the attributable fractions based upon the point estimates of the age-adjusted odds ratios and the assumption of constant prevalence of orthostatic hypotension. About 24.6 percent (95% CL: 19.0, 27.2) of the cases of orthostatic hypotension were attributed to those with plaque or stenosis who used anti-hypertensive medication and about 15.1 percent (95% CL: 0.0, 22.6) to plaque or stenosis who did not use anti-hypertensive medication. Thus, 40 percent of the cases of orthostatic hypotension could be attributed to plaque or stenosis. We estimated that 2.8 percent (95% CL: 0, 4.4) of orthostatic hypotension cases could be attributed to those with "no lesions" who did not use antihypertensive medication, 4.5 percent (95% CL: 0, 5.8) to those with "any thickening" who did not use antihypertensive medication, and 0.4 percent (95% CL: 0, 6.3) to those with "no lesions" who did not use anti-hypertensive medication. Overall, about 50 percent of all cases of orthostatic hypotension could be attributable to the five different categories of carotid wall thickening and anti-hypertensive drug use (40 percent of the total attributable fraction was due to plaque or stenosis alone). The other 50 percent could not be attributed to carotid arterial wall thickening or anti-hypertensive drug use.

In the final age-adjusted model (Table 4) the plaque or stenosis group was subdivided by type of anti-hypertensive drug use with the same reference group as above, i.e., those without any lesions in the carotid artery wall. Among those with plaque or stenosis the use of diuretics by themselves or the combined use of beta-blockers and diuretics had an odds ratio more than 15 times greater than the reference group. These were statistically significant relationships in spite of the small numbers in these drug categories.

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Figures and Tables

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Figure 1. Age-specific prevalence (percentage) of orthostatic hypotension.

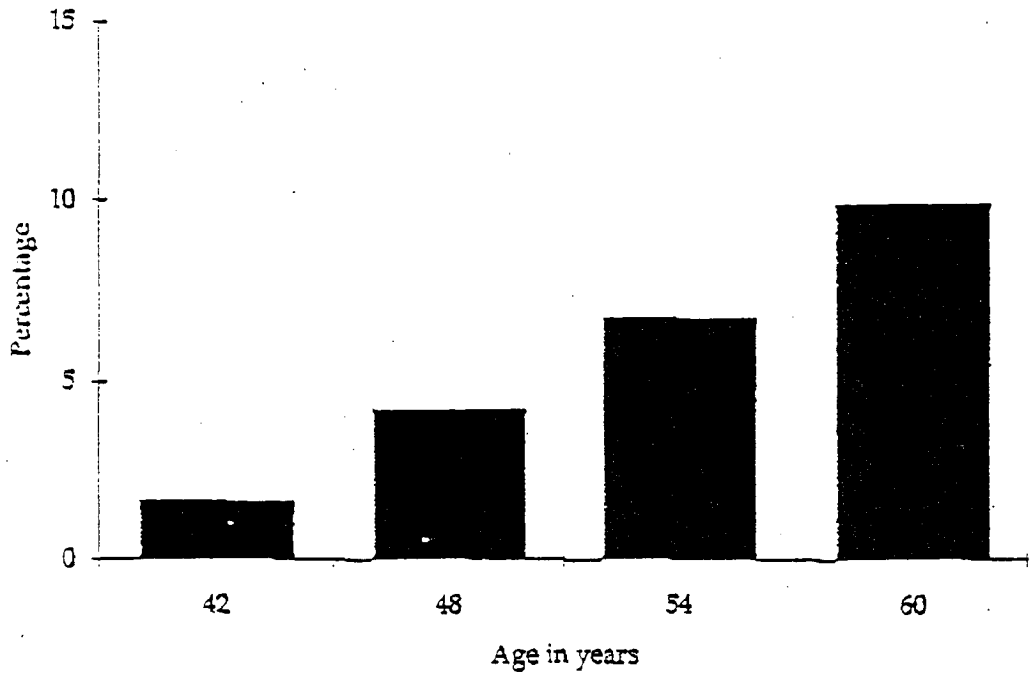

Figure 1. Age-specific prevalence (percentage) of orthostatic hypotension (95% CL are listed in text).

Table 1. Orthostatic hypotension prevalence by categories of carotid artery wall thickness stratified by anti-hypertensive medication (Rx) use.

Category of carotid wall thickness	*Persons*	*Prevalence (%) orthostatic hypotension (95% CL)*
No lesions		
No anti-hypertensive Rx	561	2.7 (1.6, 4.4)
Anti-hypertensive Rx	58	6.9 (2.7, 16.4)
Any thickening		
No anti-hypertensive Rx	229	3.5 (1.8, 6.7)
Anti-hypertensive Rx	44	11.4 (5.0, 24.0)
Plaque or stenosis		
No anti-hypertensive Rx	307	7.5 (5.0, 11.0)
Anti-hypertensive Rx	116	19.8 (13.6, 28.0)
Total	1,315	5.9 (4.8, 7.3)

[1] *These are derived from a logistic model which included only the listed variables.*

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Table 2. Odds ratios for orthostatic hypotension by category of carotid wall thickness, stratified by anti-hypertensive medication (Rx), adjusted for various risk factors.

Category of carotid wall thickness/Rx use (No.)	OR (95% CL)[1] Model 1	OR (95% CL)[1] Model 2	OR (95% CL)[1] Model 3	OR (95% CL)[1] Model 4	OR (95% CL)[1] Model 5	OR (95% CL)[1] Model 6	OR (95% CL)[1] Model 7
No lesions							
No anti-hypertensive Rx (581)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Anti-hypertensive Rx (58)	2.69 (0.86, 8.41)	2.27 (0.72, 7.18)	2.44 (0.66, 9.00)	2.23 (0.70, 7.08)	2.20 (0.71, 7.14)	2.27 (0.72, 7.19)	2.20 (0.68, 7.16)
Any thickening							
No anti-hypertensive Rx (229)	1.32 (0.55, 3.15)	1.04 (0.42, 2.56)	1.04 (0.42, 2.56)	1.04 (0.42, 2.55)	1.04 (0.42, 2.56)	1.03 (0.42, 2.54)	1.02 (0.42, 2.52)
Anti-hypertensive Rx (44)	4.67 (1.61, 13.51)	3.42 (1.14, 10.27)	3.66 (1.03, 13.07)	3.32 (1.09, 10.01)	3.35 (1.11, 10.17)	3.41 (1.14, 10.23)	3.29 (1.07, 10.05)
Plaque or stenosis							
No anti-hypertensive Rx (307)	2.94 (1.51, 5.74)	2.05 (0.98, 4.29)	2.05 (0.98, 4.30)	2.02 (0.96, 4.25)	2.04 (0.97, 4.28)	2.04 (0.97, 4.26)	1.91 (0.89, 4.09)
Anti-hypertensive Rx (116)	9.00 (4.53, 17.89)	6.05 (2.81, 13.05)	6.49 (2.45, 17.20)	5.85 (2.62, 12.94)	5.96 (2.73, 12.97)	5.90 (2.74, 12.70)	6.02 (2.75, 13.14)
Total (1,315)							
Log likelihood ratio test #1	*reference*	*p<.01 v*					
Log likelihood ratio test #2	-	*reference*	*p=0.82*	*p=0.98*	*p=0.80*	*p=0.07*	*p=0.19*

[1] Unadjusted odds ratios (OR) and 95 percent confidence intervals (95% CL) are from models which include all the variables listed.

Model 1: Crude

Model 2: Age adjustment.

Model 3: Hypertension history and age adjustment.

Model 4: Cardiovascular disease history (angina, myocardial infarction, claudication, congestive heart failure, cardiomyopathy, and age adjustment.

Model 5: Diabetes history and age adjustment.

Model 6: Psychiatric or neurohormonal disease history (mild mental problems, epilepsy, hyperthyroidism) and age adjustment.

Model 7: Body mass index, smoking, alcohol, and age adjustment.

Table 3. Age-adjusted odds ratios for orthostatic hypotension by categories of carotid artery wall thickness stratified by anti-hypertensive medication (Rx) use.showing three different contrasts

Category of carotid wall thickness	*Age-adjusted Odds ratios[1] (95% CL)*		
	COLUMN 1	COLUMN 2	COLUMN 3
	Carotid wall thickness/Rx use effect	Carotid wall thickness effect among Rx users	Rx effect per carotid wall thickness
No lesions			
No anti-hypertensive Rx	1.00 (reference)		1.00 (reference)
Anti-hypertensive Rx	2.27 (0.72, 7.18)	1.00 (reference)	2.27 (0.72, 7.18)
Any thickening			
No anti-hypertensive Rx	1.04 (0.42, 2.56)		1.00 (reference)
Anti-hypertensive Rx	3.42 (1.14, 10.27)	1.51 (0.38, 6.03)	2.95 (1.58, 5.52)
Plaque or stenosis			
No anti-hypertensive Rx	2.05 (0.98, 4.29)		1.00 (reference)
Anti-hypertensive Rx	6.05 (2.81, 13.05)	2.67 (0.86, 8.28)	3.28 (1.02, 10.60)

[1]*These are derived from a logistic model which included only the listed variables.*

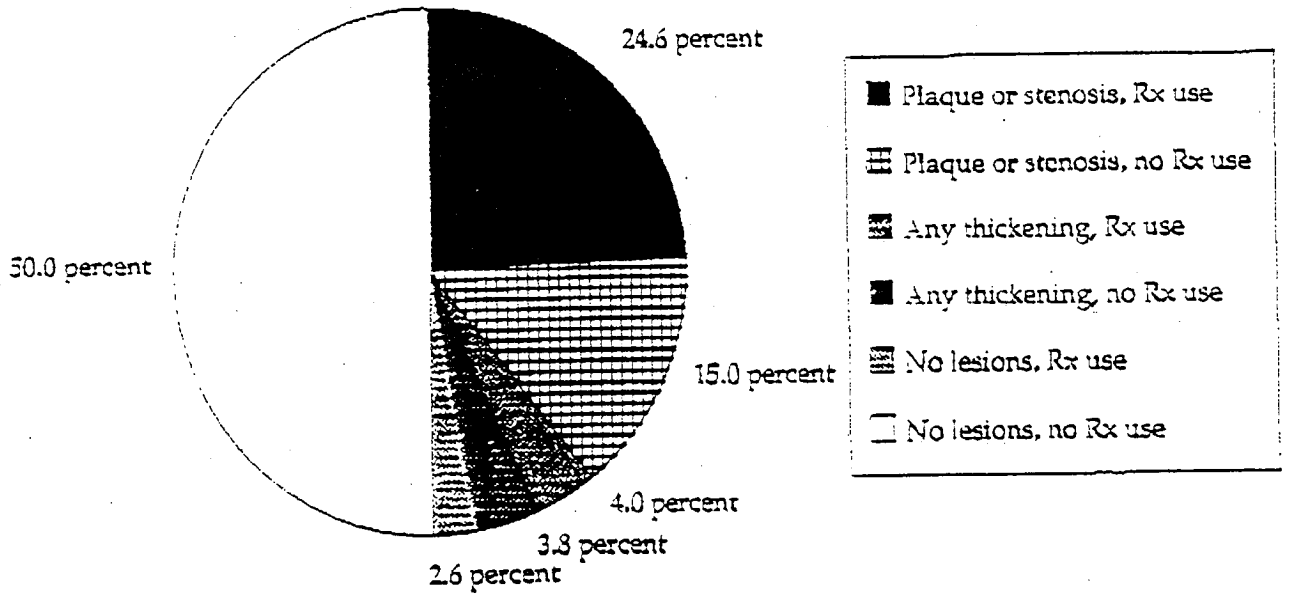

Figure 2. Attributable fractions for orthostatic hypotension based upon odds ratios for age-adjusted categories of carotid arterial wall thickness and use of anti-hypertensive medication (95% CL are listed in text).

Table 4. Association between orthostatic hypotension and categories of carotid wall thickness. Table is stratified by anti-hypertensive medication use (Rx) in both the "no lesion" and the "any thickening" category, and class of anti-hypertensive medication in the "plaque or stenosis" category.

Category of carotid wall thickness	*Persons*	*Percentage*	*Odds ratio[1] (95% confidence limits)*
No lesions			
No anti-hypertensive Rx	561	42.7	1.00 (reference)
Anti-hypertensive Rx	58	4.4	2.24 (0.71, 7.08)
Any thickening			
No anti-hypertensive Rx	229	17.4	1.02 (0.42, 2.51)
Anti-hypertensive Rx	44	3.3	3.33 (1.11, 10.01)
Plaque or stenosis			
No anti-hypertensive Rx	307	23.3	1.99 (0.95, 4.16)
Unknown drug	40	3.0	3.23 (1.04, 10.04)
Beta-blocker	57	4.3	5.71 (2.32, 14.02)
Diuretics	5	0.4	17.05 (2.57, 113.05)
Beta-blocker and Diuretics	14	1.1	14.61 (4.20, 50.82)
Total	1,315	100.0	-

[1] *These are derived from a model which included all the listed variables.*

Discussion

The mean postural drop in systolic blood pressure was about 2.0 mm Hg and the mean postural increase in diastolic blood pressure was over 7.0 mm Hg. This general pattern is in agreement with carefully controlled tests on young individuals (20 to 35-year-old healthy males) where systolic blood pressure essentially remained unchanged and diastolic blood pressure rose about 12 to 17 percent (32). Because the arm position during the standing blood pressure measurement was below heart level, the standing blood pressure would be biased upward (33), thus, the orthostatic hypotension prevalence in our study may be slightly under-estimated. In spite of this problem and the fact that it is often believed that orthostatic hypotension is a disease of the elderly, we found a surprisingly large proportion of the disorder in this middle-aged male population. Similar to other studies in elderly populations we observed an increase in the prevalence of the disorder with age.

Among those who were not on medication, the group with plaque or stenosis, a risk of orthostatic hypotension, marginally significant, was twice that of those with no lesions of the carotid wall. This supports the hypothesis that carotid wall thickening may be associated with the development of orthostatic hypotension, a finding consistent with the results from an older population from the Cardiovascular Health Study (34). Our results show, moreover, that the relationship is consistently heightened in those using anti-hypertensive medication. Subjects using antihypertensive medication were up to three times more likely to have orthostatic hypotension than those not taking anti-hypertensive medication within categories of carotid wall thickness. Indeed, among all cases of orthostatic hypotension in the population from which this sample was drawn, it was estimated that while 15 percent of them could be attributed to plaque or stenosis alone, 25 percent could be attributed to the joint effect of anti-hypertensive medication use and plaque or stenosis of the carotid artery.

There are three general possibilities for this apparent "drug effect" on orthostatic hypotension. One, the drug itself caused the orthostatic hypotension. Two, an underlying condition, for which anti-hypertensive drug use is only a proxy, caused the orthostatic hypotension. Three, a diagnosis of orthostatic hypotension itself may have led to the use of antihypertensive drugs. The third explanation can be quickly rejected, because it is highly unlikely that middle-aged Finnish men are being treated for asymptomatic orthostatic hypotension (none of our cases reported feeling faint upon

standing). This observational study does not allow us to definitively sort out the other two possibilities, but we can offer some thoughts based on the orthostatic hypotension literature.

Several clinical trials have revealed that certain classes of antihypertensive medication, especially alpha blockers, are associated with orthostatic hypotension (35, 36). These same kinds of studies show that beta-blockers have a protective effect (37,38). The evidence on diuretics is mixed (39,40, 41). None of our subjects reported using alpha blockers, indeed, they were not routinely used in Finland when the study was undertaken. We observed an increased effect of carotid atherosclerosis on orthostatic hypotension among those using diuretics alone, beta blockers alone, and diuretics and beta blockers together. The beta-blocker finding is problematic given the belief that beta-blockers are thought to protect against orthostatic hypotension, unless the beta-blocker effect is masked by some underlying disease. The effect of diuretics was quite strong and it would be hard to argue that this class of drugs was simply a marker of an underlying disease.

In an observational population study it is difficult to isolate the effect of drugs on orthostatic hypotension as underlying diseases may be confounders. High blood pressure or hypertension itself is thought to be associated with orthostatic hypotension but adjusting for history of hypertension did not affect the results. Diabetes is often related to orthostatic hypotension due to autonomic nervous system neuropathy (including mitigation of baroreceptor function) and/or large vessel lesions (atherosclerosis) (42). However, adjusting for self-reported diabetic status did not alter the odds ratio in the plaque or stenosis group, though self-reported diabetes is probably not a very sensitive way to measure neuropathy.

It may also be that carotid wall thickness is only one indication of a more generalized atherosclerotic process and problems with arterial distensibility, conditions that may lead a physician to prescribe anti-hypertensive drugs. However, adjusting the logistic model for history of cardiovascular diseases (besides hypertension) did not markedly change the age-adjusted odds ratio. Similarly, pulse pressure, a possible indication of arterial stiffening and distensibility problems (43), did rise with age, as predicted, but it was not associated with orthostatic hypotension. Robinson has suggested that individuals with orthostatic hypotension may have reduced numbers of alpha$_2$-receptors on blood vessel walls (44). This would imply a reduced ability of the vessels

to act upon baroreceptor signals. Unfortunately, the role of arterial wall thickening on the numerical reduction of alpha$_2$-receptors can not be explored in this data set.

In conclusion, this study supports the hypothesis that carotid wall thickening is a risk factor for orthostatic hypotension. The study further suggests that the prevention or regression of plaque or stenosis could theoretically lower the incidence of orthostatic hypotension in middle-aged and elderly populations by 40 percent. This study also suggests that antihypertensive medication may potentiate the impact of plaque or stenosis in the carotids on the occurrence of orthostatic hypotension. These results seem to argue for the monitoring of orthostatic hypotension in patients with significant atherosclerotic changes in the carotids who are also using beta-blockers or diuretics. To further assess biological synergy, the effect of various drugs on orthostatic hypotension should be examined in randomized clinical trials among individuals with ultrasound evidence of plaque or stenosis.

I disagree— this is FAR too strong. While a clinical trial would be the best (only) way to really address the question, it is way to premature. the only statement I would be comfortable with here would be something about the need for further study.

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