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THE ASSOCIATIONS OF SUBCLINICAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE WITH HIP FRACTURE RISK AND BONE MINERAL DENSITY IN ELDERLY ADULTS:

The Cardiovascular Health Study

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Abstract

Introduction: Clinically recognized cardiovascular disease (CVD) is associated with osteopenia and hip fracture risk, but the relationship of subclinical atherosclerosis to bone health is not certain.

Methods: We followed 3385 participants from the Cardiovascular Health Study (mean age 74.7±5.3 years) with a median time to fracture of 12.1 years who underwent baseline carotid artery and aortic wall ultrasound scanning and ankle brachial blood pressure index (ABI) determinations. A subset underwent bone mineral density (BMD) testing.

Results: There were 494 hip fractures during follow up. Among persons without clinical CVD, an average standard-deviation increase in a composite score of maximal common and internal carotid artery intimal medial thickness (cIMT) was associated with increased risk of hip fracture [(HR 1.18 [1.04, 1.35]), even though cIMT was positively associated with BMD. Neither aortic wall thickness nor ABI were associated with hip fracture risk or BMD. Among participants with clinical CVD, cIMT and aortic wall thickness, but not ABI, were associated with increased hip fracture risk.

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Conclusion: Subclinical cIMT is associated with an increased risk of hip fractures despite being associated with increased BMD. This finding suggests that vascular health, even in its early stages, is linked to bone health, by pathways other than BMD.

Keywords

subclinical atherosclerosis; bone mineral density; hip fracture; risk

INTRODUCTION

Epidemiological studies suggest an association between clinical cardiovascular disease (CVD) and osteoporotic fracture risk (1–6). Given that clinical CVD and fractures are end-stage disorders preceded by subclinical disorders – atherosclerosis that is neither symptomatic nor clinically recognized, and osteoporosis, respectively – these subclinical disorders may also be related to one another. Both trabecular bone loss (7) and early atherosclerotic lesions (8) begin in the third decade of life. Also, both conditions are related to hypertension, a risk factor for atherosclerosis, and for low bone mineral density (BMD) (9, 10).

Most of the studies that have examined the association of subclinical atherosclerosis with fracture risk have focused on vascular calcification as the marker of vascular disease (1–4). Calcification of the fibrous capsule of an atherosclerotic plaque or of the medial layer of the arterial wall is a process different from thickening of the intima and media, plaque formation, and vessel stenosis (11, 12). Less has been written on the association of subclinical vascular disease with fracture risk, irrespective of calcification. The results of these analyses have been inconsistent, with many studies suggesting both a positive association or no association (see refs 1, 2, and 4 for past summaries; see Appendix Table 1 for a summary of recent studies). Part of this inconsistency may be due to prior studies examining subclinical vascular disease in the presence or absence of clinical CVD and examining middle-aged and older age groups together. Also, most studies have been cross-sectional.

Here, we examine, in a cohort of older U.S. adults, the longitudinal associations of several subclinical measures of atherosclerosis, in the absence of clinical vascular disease, with incident hip fracture risk. We also examine, in a sub-cohort, subclinical atherosclerosis in the absence of clinical CVD with BMD. Finally, in sensitivity analyses, we examine the associations of subclinical CVD with hip fracture risk and BMD in persons with concomitant clinical CVD.

METHODS

Participants for this study were from the Cardiovascular Health Study (CHS), a population-based, longitudinal study of coronary heart disease and stroke in adults aged ≥ 65 years (13). Participants enrolled from four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. An age- and gender-stratified random sample of individuals was drawn from Medicare eligibility lists. A total of 5201 participants were recruited in 1989–1990 and 687 in 1992–1993, the

latter providing additional representation of African-Americans. All participants gave informed consent upon study entry. All clinical sites received institutional review board approval annually. During follow-up, participants were seen in clinic annually and had telephone contact annually at the midpoint between clinic visits until 1998/1999, after which all contacts were semi-annual phone calls.

Clinical CVD in 1992/1993 was defined as: 1) cardiac disease — myocardial infarction, symptoms of heart failure (HF), angina pectoris, use of nitroglycerin, coronary artery bypass graft surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA), insertion of a pacemaker, or known atrial fibrillation; 2) cerebrovascular disease (CBD) — stroke or transient ischemic attack; 3) peripheral arterial disease (PAD) — intermittent claudication, history of surgery for PAD, or people with markedly elevated ankle brachial index (ABI) values, >1.4 .

Subclinical CVD was defined as any of the following in the absence of clinical CVD. Tests for subclinical CVD were performed in 1992/1993.

Carotid Artery Disease (CD) —

Duplex ultrasonography of the carotid arteries was performed with a Toshiba SSA-270A (Toshiba American Medical Systems, Tustin, CA) equipped with a 5.0 MHz transducer. Two-dimensional brightness mode (B-mode) imaging was used to detect thickening of the arterial wall, disruption of normal wall interfaces, and development of focal plaques bilaterally. Quality of data was assessed through periodic duplicate studies to assess intra- and inter-technician reproducibility of Field Center and Reading Center technicians. Images obtained included a single lateral view of the distal common carotid artery showing the near and far walls, and three views of the carotid bulb or proximal internal carotid artery centered on the site of maximum wall thickening (13).

The maximal, rather than the mean, IMT was used since maximal IMT has a stronger relationship to CVD risk factors than mean IMT in CHS (14). We averaged the maximal IMT of the near and far walls bilaterally for both the common (CCA) and internal (ICA) carotid arteries and then averaged these two measurements after standardization (subtraction of the mean and division by the standard deviation for the measurement) ($[(\max \text{ ICA IMT} - \text{mean ICA IMT}) / \text{SD} + (\max \text{ CCA IMT} - \text{mean CCA IMT}) / \text{SD}] / 2$) (15). Fracture results are reported per one-unit increase in this derived variable (an averaged mean standard deviation). For descriptive purposes (Table 1), we defined CD as the presence of at least one of the following: increased common and/or internal carotid artery IMT (>80 th percentile of each sex and race; CCA >1.22 mm, ICA >1.88 mm) or carotid artery stenosis $>25\%$).

Peripheral Arterial Disease —

Trained technicians performed duplicate resting measurements of systolic blood pressure in the right arm and both legs with a standard mercury sphygmomanometer and an 8 MHz Doppler probe attached to a double-headed stethoscope arms according to standard protocol (13). The correlations for each duplicate blood pressure were left leg, 0.97; right leg, 0.97; and right arm, 0.95 (16). The ABI was calculated as the lower of the ratio of the average of

two systolic blood pressure measurements in each lower extremity divided by the systolic blood pressure in the right arm. Results are reported as an increase of 1 unit in ABI (e.g., comparing ABI of 0.8 to 1.8). For descriptive purposes, PAD was defined as ABI <0.9.

Aortic wall thickness —

In 1992–1993 (during the 3rd and 4th years of CHS), 4734 CHS participants had an abdominal aortic ultrasound. B-mode gray-scale images of the abdominal aorta in the longitudinal and transverse projections were obtained by trained ultrasonographers. The scanner was a Toshiba SSA 270A color Doppler duplex imager with a 3.75-MHz convex probe (17). Scans were recorded on Super VHS videotape and later scored by a reader. Measurements were calculated by using a specially designed computer program (18). The infra-renal measure of aortic diameter was determined by the site of the maximum diameter aortic artery (lumen plus wall) below the renal arteries. The aorta wall thickness (AWT), in millimeters, was measured as the distance from the outer to the internal wall from abdominal aorta ultrasound (17). All scans were read by experienced readers blinded to clinical information and subsequently were reread at a central location by a single vascular physician who was blinded to the participant's cardiovascular history. Results are reported as per 1 mm increase in AWT of both walls of the aorta.

Hip Fracture Ascertainment: CHS prospectively gathered all hospitalization data, including discharge summaries, from participants every 6 months. To ensure completeness of hospitalization records, data were checked against Medicare claims data to identify any unreported hospitalizations. Such ascertainment results in greater sensitivity for detection of hip fractures than self-report (20). Incident hip fractures were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes (820.xx). If a motor vehicle accident (E810.xx-E825.xx) was concurrent, the hip fracture was not classified as an event. Follow-up for incident hip fracture occurred from the 1992/1993 clinic visit until incident hip fracture, death, loss to follow-up, or until June 30, 2013.

DXA Scanning: In 1994/1995, a subset of the cohort (n=1575) underwent dual x-ray absorptiometry (DXA) testing in two of the CHS clinical sites. The DXA sub-cohort was younger and reported better health than the participants who did not have DXA testing (21). Total hip, femoral neck, lumbar spine (LS), and whole-body BMD in grams/cm² were measured (QDR 2000 or 2000+; Hologic, Inc, Bedford, MA). All scans were completed using the array beam mode. Scans were read blindly at the University of California, San Francisco reading center with Hologic software version 7.10. The coefficient of variation for total hip BMD was <0.75%.

Cohort for Analysis: At the baseline year (1992/1993), 5265 CHS participants from the original and African American cohorts were alive and agreed to participate. Of these, 1570 (29.9%) had one or more forms of clinical CVD. Of the 3690 remaining participants, 362 (9.8%) had missing data on subclinical CVD in at least one of the three assessed vascular beds. This left 3385 participants with information on CD, 3313 on ABI, and 3261 on AWT. Follow up was up to June 30, 2013 (95th percentile of follow up 20.75 years)

Statistical Methods: Analyses were done with men and women together and separately, given the large sex differences in hip fracture rates and different pathways for fracture development between men and women. We described the population using means and standard deviations for continuous variables and percentages for binary and categorical variables. Cox proportional hazards models were constructed to examine the association of each measure of subclinical CVD with incident hip fracture risk. Models were adjusted for risk factors shared by bone and vascular disease - age, race, diabetes, hypertension, a history of falls in the 6-months prior to baseline, estimated glomerular filtration rate (eGFR) <60 ml/minute/1.73m², current/past smoking, alcohol use, and hormone replacement therapy use in women. Results are reported per one-unit increase in ABI, per increase in one average standard deviation increase of CD, and for 1 mm increase in thickness of both walls of the aorta (AWT). To determine whether the association of subclinical CVD with fracture risk weakened with duration of follow up (22) analyses were repeated with 5 years follow up and 10 years follow up. To put our CD findings into context, we also estimated the risk of clinical CVD outcomes for an increase of one average standard deviation increase of CD.

We used linear regression analysis to estimate the association between subclinical CVD and four BMD sites. Results are reported as the change in BMD (of 10⁻² grams/cm²) per one-unit increase in ABI, per increase in one average standard deviation increase of CD, and for 1 mm increase in thickness in both walls of the aorta.

For robustness, we also examined the corresponding associations of subclinical CVD with fracture risk and BMD among participants with clinical CVD. Owing to small values, β estimates for BMD were multiplied by 100 for easier reading.

Analyses were performed using R software (23).

RESULTS

Baseline characteristics of the cohort without clinical CVD and with measures of subclinical CVD available from all three vascular beds are shown in Table 1. Approximately two-thirds were women and the mean age was 75.7 years. Mean systolic and diastolic blood pressures, mean BMI, and mean cognitive function were normal or near normal; most respondents reported good health (>80%). Approximately 20% had an eGFR <60 ml/minute/1.73m² and 13% had diabetes.

Only 9.1% of participants had an ABI <0.9, while 48.6% had some form of CD (as a dichotomous variable). Mean maximal CCA IMT was 1.06 [SD, 0.21] mm; ICA IMT was 1.37 [SD, 0.53] mm. Mean AWT was 2.3 [SD, 1.05] mm. Men had more subclinical CVD than women.

Risk of Hip Fracture by Subclinical CVD:

Median time to fracture was 12.1 [IQ, 7.1, 18.1] years, during which 494 incident hip fractures occurred (2320 women with 370 fractures; 1301 men with 124 fractures).

Hazard ratios for hip fracture risk by types of subclinical CVD are shown in Table 2. Initial and progressive adjustments attenuated the association of all forms of subclinical CVD with

hip fracture risk. Nonetheless, each standard deviation increase in maximal carotid IMT thickness was associated with a HR of 1.18 (1.04, 1.35) ($p=.01$) for hip fracture risk. For comparison, the risk of CVD events during follow-up using the same CD variable was approximately twice as high [HR 1.34 (1.26, 1.42) ($p<0.001$)]. ABI and AWT were not significantly associated with hip fracture in any models. In sex-stratified analysis, the CD association was significant in women (HR 1.23, 95% CI 1.05, 1.43), but not in men (HR 1.04, 95% CI 0.80, 1.35) with a large overlap in confidence intervals.

When separate analyses were performed limiting follow up duration to 5 years and then 10 years - approximately similar coefficients of magnitude were obtained, though there was loss of significance at 5 years owing to lower power (99 fractures by year 5 of follow up; 254 fractures by year 10 of follow up) (Appendix, Table 2).

Among the 1570 participants with clinical CVD, 161 fractures occurred (106 in 756 women, 55 in 814 men) (Table 3). In this subset, CD and AWT both were significantly associated with higher hip fracture risk, but ABI was not. Men and women in this sub-cohort had similar HR estimates.

Association of Subclinical CVD with BMD:

A one standard deviation increase in the composite CD values was associated with higher BMD values in the total hip, total body, LS, and the femoral neck (grams/cm²) (Table 4). In general, women had higher regression estimates than men. AWT also was positively associated with BMD. There was no association of ABI with BMD.

In the sub-cohort with clinical CVD, we observed no statistically significant association of CD with BMD (data not shown).

DISCUSSION

In this prospective study of older adults, subclinical CD was associated with a statistically significant increased risk of hip fracture among persons free of clinical CVD independent of its association with higher BMD. This finding was statistically significant after adjustment for fall risk and other possible confounding factors. AWT was associated with higher BMD and higher risk of hip fracture only among participants with clinical CVD, and ABI was not associated with BMD or fracture risk in either group.

Prior studies of cIMT have mostly examined its association with BMD using cross-sectional or case-control designs. Some studies showed positive associations and others did not (see ref 2, Table 3; ref 4, Table 5; Appendix, Table 1). Many of these studies did not exclude individuals with clinical CVD and were done in populations of both middle-aged and older adults. As such, our findings regarding the association of subclinical cIMT with BMD in several skeletal sites and in a relatively homogenous age group are unique. Regarding the association of subclinical cIMT with fracture risk, we are aware of only two prior cross-sectional studies. In a study of 122 middle-aged women with systemic lupus erythematosus of 11 years duration, cIMT measurements did not differ according to the presence or absence of vertebral fractures (24). In a study of 195 post-menopausal women with

osteopenia or osteoporosis (mean age ~65 years, 13–16 years after menopause) the percentage of women with vertebral fractures was significantly higher in subjects with echogenic carotid plaques than in those without (27% vs. 11%, respectively; $P < 0.05$), though there was no difference in BMD of the spine and hip (25). Our prospective results regarding hip fracture risk in association with a composite measure of cIMT extend these previous results.

The increased risk of hip fracture with CD did not occur through reduced BMD. On the contrary, CD was positively associated with increased BMD. Most studies examining the association of subclinical CVD with BMD in older adults report BMD to be reduced (1–4). There is, however, precedence for our finding. In a study of Mexican Americans, mean carotid IMT was weakly but positively associated with hip and distal radial BMD in women <60 years of age (26). In the Multi-Ethnic Study of Atherosclerosis (MESA), ICA IMT was not associated with CT derived volumetric BMD of the spine in women (27). In the Tromsø study, BMD was not associated with non-calcified carotid plaques (28). In a study of 3366 premenopausal women (mean age 48.1 years) from the United Kingdom (29), total body and hip BMD were significantly and positively associated (albeit weakly) with mean carotid IMT.

In the absence of lower BMD, several other factors may link subclinical CD with hip fracture. Even in a cohort without known clinical CVD, increased cIMT is associated with subclinical lacunar infarctions (30), which are associated with gait abnormalities that lead to falls (31). Increased cIMT is associated with cognitive impairment, which also can lead to falls (32, 33). However, adjustment for self-reported falls in the 6 months preceding baseline did not meaningfully impact our results. Also, cIMT thickness is associated with skin auto-fluorescence, a non-invasive marker for advanced glycation end-product accumulation, a marker of oxidative stress independent of traditional CVD risk factors (34, 35). We have shown that elevated levels of the glycation end-product carboxymethyl-lysine (CML) predict hip fracture risk independent of BMD (36). cIMT is also positively related to serum levels of C-terminal telopeptide of type I collagen, a marker of increased bone resorption (37) and with reduced perfusion of the vertebral skeleton (38).

To our knowledge, ours is the first study to examine AWT and risk of hip fracture. We observed associations comparable to those for CD among participants with clinical CVD. Together with our findings on ABI, these results suggest that there may be characteristics of specific vascular beds that particularly relate to hip fracture risk, while also suggesting common links across both carotid and aortic thickening.

We did not find an association between ABI and fracture risk or BMD. Several previous studies have reported a weak association or no association of ABI with BMD or hip fracture risk (27, 38–41). One possible explanation for our finding of no association may be the low prevalence of PAD (9.1%) in the cohort. However, even when treated as a continuous variable to maximize power, no association emerged. Alternatively, subclinical CVD in the lower extremities may relate to bone disease differently than carotid artery wall thickening owing to differences in hemodynamics, risk factors, and shear forces. Finally, ABI is a functional measure of arterial blockage related to wall thickening, abnormal vascular

function, and collateral flow; CD is an anatomic measure (42). Unlike CD and AWT, ABI tended to be associated, albeit not significantly, with lower BMD.

Strengths of this study include a well characterized prospective cohort and accurate measures of subclinical CVD and BMD. Many hip fractures were confirmed by medical chart review and Medicare claims data over a long follow up period. Limitations include lack of data on vascular calcification and stiffness and no data on subclinical coronary artery disease since coronary CT scans were not routinely performed. Last, DXA scanning was performed 1–3 years after vascular testing and only in a subset of the cohort.

In conclusion, the association of pre-clinical atherosclerosis, BMD, and fracture risk in older, relatively healthy adults, is complex. Subclinical carotid artery disease is associated with increased hip fracture risk, suggesting that the association of bone disease and vascular disease begins early on. The increased risk is not mediated by lower BMD, since BMD is higher in the presence of CD. Neither subclinical ABI nor AWT are associated with fracture risk or BMD. Cumulatively, these results highlight the need to explore further the pathways that link these conditions which may offer insight into the prevention of hip fracture and CVD, two highly morbid and common conditions of older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BRIEF SYNOPSIS

In the absence of clinically recognized cardiovascular disease, increased carotid artery intimal medial thickness was associated with higher hip fracture risk in older adults, despite its association with higher bone mineral density (BMD). Low ankle brachial index and aortic wall thickness were not associated with fracture risk or BMD.

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Table 1:

Baseline characteristics of the Cardiovascular Health Study cohort without clinical cardiovascular disease.

	Total N=3623	Women N=2320	Men N= 1303
Demographic Characteristics			
Age (years)	75.7±5.3	74.5±5.2	75.0±5.5
Black race (%)	17.0	16.9	17.0
Smoker (%)			
Current	10.1	9.8	10.5
Former	41.9	31.9	59.6
Never	48.0	58.3	30.0
Self-reported good health (%)	83.3	82.5	84.8
Fall 6-months prior to baseline (%)	15%	18%	9.6%
Difficulty with activities of daily living (%)	8.9	10.3	6.3
Physical activity (%)			
None / little	22.9	26.2	17.0
Moderate	53.4	55.6	49.5
Strenuous	23.7	18.2	33.5
Education >12 years (%)	45.7	43.6	49.5
Alcohol (drinks per week) (%)			
None	55.0	59.9	46.1
1-7	33.9	32.6	36.2
>7	11.1	7.4	17.7
Health Characteristics			
Systolic blood pressure (mmHg)	136.7±20.9	136.8±21.0	136.4±20.8
Diastolic blood pressure (mmHg)	72.0±11.2	70.9±11.1	74.0±11.1
BMI (kg/m ²)	26.8±4.7	27.0±5.2	26.6±3.8
Mean eGFR _{cyst} (ml/minute/1.73m ²)	75.1±18.4	76.5±18.5	72.7±17.8
eGFR _{cyst} <60 ml/minute/1.73m ² (%)	20.4	20.1	20.9
Modified Mini Mental State Exam score	90.4±7.2	90.7±9.7	89.7±9.7
Diabetes (%)	13.3	11.8	16.0
Medication Use (%)			
Steroids	2.1	2.1	2.0
Loop diuretics	3.7	4.3	2.6
Thiazides	16.8	19.0	12.7
Beta blockers	8.7	8.9	8.2
Laboratory Data (mean ± std dev)			
Fasting glucose (mg/dl)	106.6±34.1	105.2±33.7	109.1±34.8
Fasting insulin (IU/ml)	12.8±16.2	12.8±15.5	12.9±17.4
LDL cholesterol (mg/dl)	127.3±33.5	130.8±33.9	121.3±32.0
HDL cholesterol (mg/dl)	54.9±14.6	58.7±14.7	48.2±11.7
Log ₂ CRP (mg/L)	1.3±1.6	1.4±1.6	1.2±1.6
Measures of Subclinical CVD			

	Total N=3623	Women N=2320	Men N= 1303
Ankle brachial index (ABI) (mean, SD) (continuous)	1.1±0.2	1.1±0.2	1.1±0.2
Peripheral artery disease (ABI <0.9) (dichotomous) %	9.1	8.5	10.0
Aortic wall thickness (AWT) mm (continuous)	2.3±1.05	2.2±0.75	2.5±1.5
Carotid artery disease (dichotomous) (%)	48.6	45.3	54.4
Standardized carotid artery disease (continuous)	-0.11±0.77	-0.22±0.74	0.08±0.8

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Table 2 –

Hazard ratios for hip fracture associated with subclinical vascular disease in the absence of clinical cardiovascular disease.

	N	Fx	All			Men			Women		
			HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
ABI *	3313	445									
Model 0			0.58	(0.29,1.15)	0.12	0.54	(0.16,1.87)	0.33	0.60	(0.26,1.36)	0.22
Model 1			0.74	(0.37,1.49)	0.40	0.76	(0.21,2.73)	0.68	0.75	(0.32,1.73)	0.50
Model 2			0.95	(0.46,1.99)	0.90	0.88	(0.23,3.35)	0.85	1.05	(0.43,2.52)	0.92
CD **	3383	455									
Model 0			1.23	(1.09,1.40)	<0.001	1.16	(0.91,1.48)	0.24	1.25	(1.08,1.45)	0.002
Model 1			1.16	(1.02,1.31)	0.03	1.08	(0.85,1.39)	0.52	1.18	(1.01,1.37)	0.04
Model 2			1.18	(1.03,1.35)	0.01	1.04	(0.80,1.35)	0.76	1.23	(1.05,1.43)	0.01
AWT ***	3261	444									
Model 0 Thickness			0.96	(0.90,1.03)	0.28	0.98	(0.88,1.09)	0.66	0.96	(0.88,1.04)	0.30
Model 1			0.96	(0.89,1.03)	0.21	0.98	(0.86,1.09)	0.65	0.94	(0.86,1.03)	0.20
Model 2			0.97	(0.90,1.04)	0.37	0.96	(0.86,1.08)	0.51	0.97	(0.88,1.06)	0.44

The hazards ratios for hip fractures are per unit increase in the predictor:

*

Per 1 unit increase in the ratio (index) of the ankle to brachial blood pressures.

**

Per one average standard deviation increase of IMT – i.e., standard deviations away from the mean IMT variable.

Per 1mm increase in both walls of the aorta.

ABI – ankle brachial index; CD – carotid artery disease; AWT – aortic wall thickness; N – number at risk; Fx – number of hip fractures

Model 0 – age, sex and race;

Model 1 – Model 0 + current smoking + alcohol (0 ref, 1–7, >7 drinks);

Model 2 – Model 1 + weight (kg) + diabetes+ hypertension+ eGFR cystatin + estrogen (females) + history of falling in the year before baseline

Table 3 -

Hazard ratios for hip fracture by subclinical vascular disease in the presence of clinical cardiovascular disease.

	N	Fx	All			Men			Women		
			HR	95%CI	p-val	HR	95%CI	p-val	HR	95%CI	p-val
ABI *	1364	144									
Model 0			0.57	(0.26,1.26)	0.17	0.70	(0.20,2.41)	0.57	0.50	(0.18,1.42)	0.19
Model 1			0.63	(0.27,1.45)	0.28	0.70	(0.19,2.52)	0.58	0.58	(0.19,1.77)	0.34
Model 2			0.84	(0.33, 2.09)	0.70	0.71	(0.18,2.85)	0.63	0.86	(0.25,3.01)	0.82
CD **	1387	146									
Model 0			1.29	(1.08,1.54)	0.006	1.27	(0.95,1.69)	0.11	1.30	(1.03,1.64)	0.03
Model 1			1.26	(1.04,1.53)	0.02	1.27	(0.95,1.72)	0.11	1.25	(0.98,1.61)	0.07
Model 2			1.25	(1.02,1.53)	0.03	1.31	(0.97,1.78)	0.08	1.18	(0.90,1.54)	0.23
AWT ***	1338	142									
Model 0			1.10	(1.05,1.16)	<0.001	1.09	(1.03,1.16)	0.007	1.15	(1.05,1.26)	0.003
Model 1			1.11	(1.05,1.17)	<0.001	1.10	(1.03,1.17)	0.006	1.14	(1.04,1.26)	0.008
Model 2			1.11	(1.05,1.17)	<0.001	1.08	(1.01,1.16)	0.027	1.15	(1.04,1.27)	0.006

The hazards ratios for hip fractures are per unit increase in the predictor:

* Per 1 unit increase in the ratio (index) of the ankle to brachial blood pressures.

** Per one average standard deviation increase of IMT – i.e., standard deviations away from the mean IMT variable.

*** Per 1mm increase in both walls of the aorta.

ABI – ankle arm index; CD – carotid artery disease; AWT – aortic wall thickness; N – number at risk; Fx – number of hip fractures

Model 0 – age, sex and race;

Model 1 – Model 0 + current smoking + alcohol (0 ref, 1–7, >7 drinks);

Model 2 – Model 1 + weight (kg) + diabetes+ hypertension+ eGFR cystatin + estrogen (females) + history of falling in the year before baseline

Table 4:

The association of subclinical carotid artery disease (CD), aortic wall thickness (AWT) and ankle brachial index (ABI) with bone mineral density in several sites categorized by sex. Results are adjusted for age, sex, black race, current smoking, alcohol (0 ref, 1-7, >7 drinks), weight (kg), diabetes, hypertension, eGFR based on cystatin, and estrogen use in women. (β estimates (grams/cm²) are multiplied by 100 for easier understanding.)

	All beta	SE	95%CI	p-val	Women beta	SE	95%CI	p-val	Men beta	SE	95%CI	p-val
Total hip												
CD	1.511	0.57	(0.39,2.63)	0.008	1.983	0.671	(0.67, 3.30)	0.003	0.66	1.06	(-1.42,2.74)	0.54
AWT	1.07	0.28	(0.51, 1.62)	< 0.001	1.39 0.347 (0.71,2.07) <0.001	0.35	(0.71, 2.07)	< 0.001	0.64	0.49	(-0.33, 1.60)	0.20
ABI	-1.27	2.96	(-7.07, 4.52)	0.67	1.25	3.67	(-5.95, 8.44)	0.74	-4.33	5.05	(-14.23, 5.57)	0.39
Total Body												
CD	1.019	0.45	(0.13,1.89)	0.024	1.29	0.53	(0.25, 2.33)	0.016	0.45	0.82	(-1.149,2.051)	0.58
AWT	0.59	0.22	(0.16, 1.03)	0.008	0.64	0.28	(0.10, 1.18)	0.02	0.51	0.38	(-0.23, 1.26)	0.18
ABI	-2.53	2.30	(-7.04, 1.99)	0.27	1.42	2.90	(-4.25, 7.10)	0.62	-6.88	3.86	(-14.46, 0.07)	0.08
LS spine												
CD	3.399	0.976	(1.49,5.31)	< 0.001	3.428	1.21	(1.05,5.81)	0.005	2.97	1.67	(-0.31,6.24)	0.08
AWT	1.74	0.49	(0.78, 2.69)	< 0.001	1.71	0.63	(0.48, 2.95)	0.007	1.75	0.78	(0.22, 3.28)	0.03
ABI	-4.75	5.03	(-14.62, 5.12)	0.35	3.00	6.60	(-9.93, 15.94)	0.65	-12.70	7.94	(-28.27, 2.88)	0.11
Femoral Neck Nck												
CD	1.331	0.51	(0.33, 2.33)	0.009	1.50	0.60	(0.32, 2.67)	0.013	0.89	0.946	(-0.97,2.74)	0.35
AWT	1.021 (0.526,1.516) <0.001	0.25	(0.526,1.516) <0.001	< 0.001	0.86	0.31	(0.25, 1.46)	0.006	1.22	0.43	(0.37, 2.07)	0.005
ABI	-1.25	2.63	(-6.40, 3.90)	0.64	-0.74	3.26	(-7.13, 5.65)	0.82	-1.82	4.49	(-10.61, 6.97)	0.69

The change in BMD for each predictor is:

Per one mean standard deviation increase of IMT – i.e., standard deviations away from the mean IMT variable.

Per 1mm increase in both walls of the aorta (AWT).

Per 1 unit increase in the ratio (index) of the ankle to brachial blood pressure.

ABI – ankle arm index; CD – carotid artery disease; AWT – aortic wall thickness.