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Measures of carotid atherosclerosis and fall-related hospitalization risk: The Perth Longitudinal Study of Ageing Women

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Abstract

Background and aims

We and others have identified links between cardiovascular conditions and poor musculoskeletal health. However, the relationship between measures of carotid atherosclerosis such as focal carotid plaque and common carotid intima media thickness (CCA-IMT) and falls remains understudied. This study was aimed to examine the association between measures of carotid atherosclerosis and fall-related hospitalization over 11.5 years in community dwelling older women.

Methods and Results

1116 older women recruited in 1998 to a five-year randomized controlled trial to examine the effect of calcium supplementation in preventing fracture and who had undertaken B-mode ultrasound in 2001 (three years after the baseline clinical visit) were included in this study. The participants were followed for over 11.5 years as Perth Longitudinal Study of Ageing Women (PLSAW). Over the follow up period, 428 (38.4%) women experienced a fall-related hospitalization. Older women with carotid plaque had 44% a higher relative hazard for fall-related hospitalization (HR 1.44; 95%CI, 1.18 to 1.76) compared to those without carotid plaque. The association persisted after adjustment for established falls risk factors such as measures of muscle strength and physical function. Per SD CCA-IMTs, mean HR (SD=0.13) 1.10; 95%CI, 1.00 to 1.21) and maximum (SD=0.15) HR 1.11; 95%CI, 1.01 to 1.22) were also associated with higher risk of fall-related hospitalizations.

Conclusions

Measures of carotid atherosclerosis are associated with a higher risk of fall-related hospitalization independent of established falls risk factors. These findings suggest the importance of vascular health when considering falls risk.

Keywords: Carotid atherosclerosis, carotid intima media thickness, falls, physical function, older women

Introduction

Falls cause approximately 37.3 million people globally to require medical attention each year [1]. Approximately 28-35% of people aged 65 years and older fall annually [2]. In older people, falls are associated with loss of functional independence, institutionalization and poorer quality of life [3]. Falling propensity is complex and to date has been associated with combination of risk factors including weak muscle strength, compromised gait and balance, visual impairment and autonomic dysfunction [4]. Growing evidence suggests that cardiovascular disease (CVD) increases falls propensity [5, 6]. Specifically, clinical conditions such as stroke [7] and heart failure [8] are associated with increased risk of falls. Additionally, measures of subclinical CVD such as arterial stiffness and abdominal aortic calcification (AAC) have been reported to be associated with weaker muscle strength [9-11] and higher risk of falls [12, 13]. Of note, muscle strength is a well-established risk factor for falls [14].

Focal carotid atherosclerotic plaque and carotid artery intima thickness (CIMT) are measures of carotid atherosclerosis, which is a surrogate marker for cerebrovascular disease [15]. Carotid atherosclerosis is also associated with increased risk of cardiovascular events [16-18] and all-cause mortality [19] independent of conventional risk factors. Additionally, CIMT is positively correlated with AAC [20].

Identifying falls risk factors and underlying mechanisms is important in risk stratification measures as well as developing and implementing targeted falls prevention strategies. To date, a few small cross-sectional studies have investigated associations between carotid atherosclerosis, and measures of muscle function [21] and falls [22]. However, the findings of these studies are inconsistent and have not investigated the most serious type of falls, being those that require hospitalization. Additionally, the temporal nature of the relationship remains uncertain. This study was aimed to examine the association between measures of carotid atherosclerosis, measures of muscle function, and long-term falls requiring hospitalization in community-dwelling older women.

Methods

Study population

The participants included community-dwelling older women recruited in 1998 to a five-year prospective, randomized controlled trial of oral calcium supplementation to prevent fractures [Calcium Intake Fracture Outcome study (CAIFOS)] [23]. For CAIFOS, 1,500 women aged over 70 years with an expected survival of beyond five years were recruited from the general population by mail using the electoral roll, which is a requirement of citizenship. All the participants were ambulant and had comparable baseline disease burden and medications with the general population of similar age, although these participants were more likely to be from higher socio-economic groups [23]. B-mode carotid ultrasound examination was undertaken in 2001 (three years after the baseline clinical visit) in 1,149 women (76.6% of the original cohort) to assess CIMT and the presence of carotid plaque. At the conclusion of CAIFOS, the participants were subsequently included in a 10-year observational follow-up, the Perth Longitudinal Study of Ageing Women (PLSAW). Women who experienced fall-related hospitalizations before carotid ultrasound measurement (from 1998 to 2001, n=33) were excluded from the analyses. This left a sample of 1,116 participants. Detailed study design is presented in **Supplementary Figure 1**.

Ethics approval

Ethics approval was obtained from the Human Ethics Committee of the University of Western Australia. CAIFOS (trial registration number #ACTRN12615000750583) and PLSAW (trial registration number #ACTRN12617000640303) were retrospectively registered on the

Australian New Zealand Clinical Trials Registry and complied with the Declaration of Helsinki. Ethics approval for the use of linked data was granted by the Human Research Ethics Committee of the Western Australian Department of Health (project number #2009/24). Written informed consent, including future access to Western Australian Health Department data, was provided by all participants.

Assessment of baseline characteristics in 1998

Body mass index (BMI) was calculated from body weight (kg) and height (cm) assessed using digital scales and a wall-mounted stadiometer respectively. For the CAIFOS trial, participants were randomized either to placebo or calcium. Smoking history was coded as non-smoker or smoked ever (if they had consumed >1 cigarette per day for more than three months at any time in their life or is a current smoker). Antidiabetic medication use (oral hypoglycemic medications or insulin) at baseline was used to assess prevalent diabetes mellitus. Lipid and blood pressure lowering medications use were verified by participants' General Practitioner where possible and were coded using the International Classification of Primary Care-Plus (ICPC-Plus) method. Physical activity levels were assessed by asking participants about any sport, recreation, and/or regular physical activities undertaken three months prior to their baseline visit. Accordingly, participants activity level was calculated using a validated method in kcal/day **[24]**. Prevalent falls were assessed by asking participants at their baseline clinical visit if they experienced a fall (yes/no) in the previous three months. Prevalent atherosclerotic vascular disease (ASVD) was obtained from primary discharge diagnoses from hospital records (1980–1998) as described previously **[25]**. Mean systolic and diastolic blood pressures were measured on the right arm with a mercury column manometer using an adult cuff after the participants have been seated in an upright position and had rested for 5 minutes. Hand grip strength and timed-up-and-go (TUG) test performance were measured at baseline (1998) and five years (2003). Detailed assessment of such measures of muscle function in this cohort have been previously described **[11]**. Weak hand grip strength (<22 kg) and impaired mobility (TUG >10.2 s) were defined based on previous work **[11]**. Fear of falls was assessed by asking participants to respond yes or no to the following questions: ''Are you afraid of falling?'' ''Do you limit any household activities because you are frightened you may fall?'' and ''Do you limit any outside activities because you are frightened you may fall?'' If answered yes to any of the three questions, the patient was classified as having afraid of falling **[26]**. Abdominal aortic calcification was assessed using digitally enhanced lateral single-energy images of the thoraco-lumbar spine using a Hologic 4500A bone densitometer (Hologic, Bedford, MA, USA) and semi-quantitatively scored from 0 to 24 (AAC24 score) as described previously **[12]**. A validated semi-quantitative food frequency questionnaire (FFQ) from the Cancer Council Victoria was used to assess dietary intake including dairy products [27]. Energy and nutrient intakes were estimated using the NUTTAB95 food composition database as described previously. Plasma 25OHD (total vitamin D) concentration was determined using a validated LC–MS/MS (Liquid Chromatography Tandem Mass Spectrometry) method at the RDDT Laboratories (Bundoora, VIC, Australia) as previously described [28]. Blood pressure was measured on the right arm with a mercury column manometer using an adult cuff and an average of three blood pressure readings was recorded. Fasting blood samples for creatinine was collected at baseline (1998). The estimated glomerular filtration rate (eGFR) creatinine was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[29] The time at which menopause occurred was assessed by asking the participants at what age they had seen their last menstrual periods. Menopause before the age of 45 years is considered early menopause.

Incident cerebrovascular accident hospitalizations for over 11.5 years were retrieved from the Hospital Morbidity Data Collection (HMDC) which provides a complete record of every participant's primary diagnosis at hospital discharge (hospital separation) using coded data from all hospitals in Western Australia. Cerebrovascular hospitalization separations were defined from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 10 and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10- AM). These codes for cerebrovascular disease, excluding hemorrhage, included: ICD-9-CM codes 433- 438 and ICD-10-AM, codes I63-I69, G45.9 [30].

Assessment of carotid plaque and CCA-IMT

Assessments of the presence of focal carotid plaque and CCA-IMT were performed in 2001 using B-mode carotid ultrasound examination by the same sonographer with an 8.0 mHz linear array transducer fitted to an Acuson Sequoia 512 ultrasound machine using a standard image acquisition protocol. The far walls of the distal 2 cm of both the left and right common carotid arteries were examined and images were taken from 3 different angles (anterolateral, lateral, and posterolateral) to account for the possibility of asymmetrical wall thickening. End-diastolic images were recorded, and a semi-automated edge-detection software program was used for image analysis. The same technician performed off-line analysis of all of the images. After an assessment of CCA-IMT and focal plaque on the right side, the process was repeated on the left side. The CCA-IMT from each of the 6 images (3 on either side) was averaged to give an overall mean and maximum CCA-IMT (measured in mm). Once IMT images were recorded, the entire carotid tree (CCA, carotid bulb, internal and external carotid) was examined for the presence of focal plaque defined as a clearly identified area of focal increased thickness (≥1 mm) of the intima-media layer. Further, based on the degree of carotid stenosis, the severity of carotid plaque was categorized into none (0% stenosis), less advanced (<25% stenosis) and advanced (≥25% stenosis) [30-32]. A short-term precision study of 20 non-trial subjects with repeat IMT measurements between 0 and 31 days apart (mean 10.3 days) was performed which yielded a coefficient of variation (CV) of 5.98% [33].

Fall-related hospitalization

Injurious fall-related hospitalizations over 11.5 years were tracked through the Western Australian Data Linkage System (Department of Health Western Australia, East Perth, Australia) and retrieved from the Western Australia Hospital Morbidity Data Collection (HMDC) [34]. Falls from standing height or less, not resulting from external force were included, ICD- 10 codes: W01-Fall on same level from slipping, tripping, and stumbling; W05-Fall involving wheelchair or scooter; W06-Fall from bed; WO7-Fall from chair; W08-Fall from furniture; W10-Falls from stairs and steps; W18-Other fall on the same level, and W19-Unspecified fall. Only falls deemed serious enough to warrant hospital admission were included here.

Statistical analysis

The primary outcome of the study was fall-related hospitalization, while the presence and severity of carotid plaque as well as CCA-IMT (per SD mean and maximum) were the exposure variables. Follow-up began on the day of their visit for the carotid ultrasound examination until the first fall, death, or the end of the study follow-up period, which ever came first. Kaplan-Meier survival curves and a log-rank test were used to assess univariate association between carotid plaque (present versus absent) and fall-related hospitalization. Cox-proportional hazards model was used for the primary analysis. Restricted cubic splines as part of Cox proportional hazard model were used to explore the nature of the relationship between CCA-IMTs and hazard ratios for fall-related hospitalization. Three models were adopted: (i) unadjusted; (ii) minimally-adjusted: age, BMI and treatment code (calcium or placebo); and (iii) multivariable-adjusted: minimally-adjusted plus smoked ever, prevalent atherosclerotic vascular disease (ASVD), diabetes and falls, statin, anti-hypertensive medication use and physical activity. Cox proportional hazards assumptions were tested on the basis of Schoenfeld residuals in R. P-values of >0.05 were recorded for the global test and individual covariates suggesting that proportional hazards assumptions were not violated.

Additional analyses

We have tested the association between the presence of carotid plaque and fall-related hospitalization after adding carotid plaque and CCA-IMTs together. Further analyses were also undertaken after excluding women with prevalent ASVD or incident cerebrovascular accident hospitalizations. Previously, an association between AAC and falls has been reported [12]. Thus, we have examined the association between AAC and falls after including AAC24 score into the multivariable-adjusted model.

As muscle function is a key predictor of falls, we included hand grip strength and TUG performance (separately and combined) when examining the relationship between carotid atherosclerosis and falls [34]. Logistic regression was used to investigate the association between carotid plaque, and weak hand grip strength and slow TUG performance assessed two years after carotid ultrasound examination was undertaken. Given a reported association between vitamin D status and fall-related hospitalization previously from the same cohort [35], we also examined the relationship between carotid plaque and falls after including baseline 25OHD status. Furthermore, we have tested the association between the presence of carotid plaque and fall-related hospitalization after including dietary calcium intake, both mean SBP and DBP, eGFR creatine and age at menopause was included into the multivariable adjusted model each at a time. All the sensitivity analyses were performed in the multivariable adjusted model. Interaction tests between the presence of carotid plaque and other falls risk factors (smoking, physical activity, prevalent ASVD, mean systolic blood pressure, antihypertensive medications, statin, hand grip strength, TUG, and fear of falling) was performed to determine whether the association between carotid plaque and fall-related hospitalizations was modified by the aforementioned risk factors in the multivariable-adjusted model. A p for interaction of

<0.1 was considered significant. Spearman *rho* correlation analyses was used to examine a correlation between CCA-IMT (mean and maximum), grip strength and TUG performance measured in 1998 and 2003.

Results

Women with carotid plaque were older, included a higher number of smokers and prevalent chronic diseases (**Table 1)**. Lipid lowering and antihypertensive medications use were also more frequent in older women with carotid plaque compared to those without carotid plaque.

Carotid atherosclerosis and falls

Over 11.5 years of follow-up (9,714 person years, 75.1 ± 2.7 years), 428 (38.4%) women experienced a fall-related hospitalization. Kaplan–Meier survival curve revealed women with carotid plaque had a higher falls risk compared to those without carotid plaque [**Figure 1**]. Cox-regression survival curve in the multivariable-adjusted model also indicated a similar finding [**Supplementary Figure 2**]. In the multivariable-adjusted model, women with carotid plaque had a 44% higher relative hazard for fall-related hospitalization, compared to those without carotid plaque [**Table 2**]. Further, women with less advanced (HR 1.38; 95%CI, 1.12 to 1.72) and advanced carotid stenosis (HR 1.61; 95%CI, 1.21 to 2.13) had higher relative hazards for a fall-related hospitalization, respectively, compared to those without carotid stenosis. Per SD mean [0.13 mm], HR 1.10; 95%CI, 1.00 to 1.21 and per SD maximum [0.15 mm], HR 1.11; 95%CI, 1.01 to 1.22) CCA-IMTs were associated with 10% and 11% increase in relative hazard for a fall-related hospitalization respectively [**Table 2**]. Restricted cubic spline curves in **Supplementary Figure 3** suggests a linear relationship between mean (p for non-linearity = 0.826) or maximum (p for non-linearity = 0.558) CCA-IMT and hazard ratio for fall-related hospitalization.

Additional analyses

The association between carotid plaque and falls persisted when added together with per SD CCA-IMT (mean or maximum separately) into the multivariable-adjusted model [**Table 3**]. However, the associations between CCA-IMTs and falls, (per SD mean HR 1.07; 95%CI, 0.98 to 1.18; and per SD maximum HR 1.08; 95% CI, 0.98 to 1.19) were attenuated. The association between carotid plaque and fall-related hospitalization remained similar after women with prevalent ASVD (n=122, HR 1.46; 95%CI, 1.18 to 1.81) or incident cerebrovascular accident hospitalizations (n=139, HR 1.40; 95%CI, 1.13 to 1.75) were excluded. The association between carotid plaque and fall-related hospitalization also remained significant after baseline AAC24 score, total vitamin D (25OH D2 & D3), dietary calcium intake, grip strength and TUG (separately or combined), both mean SBP and DBP, eGFR and age at menopause were added separately into the multivariable-adjusted model [**Table 3**].

The presence of carotid plaque was associated with a higher odds of weak muscle strength (OR 1.67; 95%CI, 1.15 to 2.41), but not slow TUG performance (OR 1.15; 95%CI, 0.86 to 1.54) [**Table 4**]. Of the risk factors examined for potential interactions with carotid plaque for fall-related hospitalization, only a significant interaction was observed with grip strength at baseline (p_{inter} = 0.005). Carotid plaque was strongly associated with fall-related hospitalizations in older women with greater grip strength (≥22 kg: HR 2.27; 95%CI, 1.58 to 3.25, <22 kg: 1.15; 95%CI, 0.90 to 1.46).

Weak, but significant correlations (ρ between 0.08 to 0.11, $p < 0.05$) between CCA-IMT (mean and maximum) and TUG performance were also noted [**Supplementary Table 1**].

Discussion

In this prospective study in community-dwelling older women, we have demonstrated that the presence of carotid plaque was associated with an increased risk of falls requiring hospitalization accounting for well-defined falls related risk factors. Risks were most pronounced in those with advanced carotid plaque (≥25% carotid stenosis), but substantial risks were noted even in those with minimal stenosis (<25%) and indeed in those with any detectable plaque. These associations remained significant even after excluding women with prevalent ASVD as well as incident cerebrovascular disease. Thus, the presence of carotid plaque should prompt clinicians to be aware falls risk in older women with carotid atherosclerosis that may benefit from preventative interventions and risk modification through lifestyle changes (e.g., exercise and nutrition).

Atherosclerosis including plaque formation are a common age-related biological process associated with blood vessel disease. Carotid plaque [36] and CCA-IMT [37] are measures of carotid atherosclerosis and have been shown to be associated with clinical CVD [38]. In this study, atherosclerotic carotid plaque was observed in almost half of the older women, and it was associated with 9.6% absolute and 44% higher relative risks for falls which are considerable. Of note, almost one in two women (43.3%) with carotid plaque had experienced fall-related hospitalization over the 11.4 years of follow-up which is a considerable burden. Given these women were over 70 years and followed for 11.5 years, it would be expected that a large proportion would be hospitalized for falls. Similarly, we have previously reported that 41% of older women with abdominal aortic calcification, a marker of advanced atherosclerosis, in this cohort (N= 1053 women, age = 75.0 ± 2.6 years, follow-up= over 14.5 years) had experienced fall-related hospitalization. Gray et al (2019) (N=80, age >70 years) also reported 42.3% self-reported falls in the last six months in older adults with carotid stenosis compared to only 14.5% for those with no stenosis.[22] Such findings overall indicate carotid atherosclerosis may provide prognostic information about the risk of future falls.

The present study builds on our previous work highlighting the impact of atherosclerotic vascular disease on falls [12] and is important because adding measures of carotid atherosclerosis, to the existing falls risk assessment tools may improve falls risk prediction. The association between carotid plaque and falls were independent of muscle function and subclinical vascular disease measures. The association between CCA-IMTs and falls also persisted after adjustment to measures of muscle function. Such findings indicate carotid atherosclerosis may provide prognostic information about the risk of future falls requiring hospitalizations. Given carotid ultrasound imaging is becoming increasingly common, the implications of these findings are two-fold. Firstly, in women undertaking carotid ultrasound this increased risk of falls should be considered. Secondly, identifying these women at higher risk of CVD and falls may lead to better targeting of lifestyle interventions in this population, particularly as the risk appears to diverge roughly four years after the measurement of carotid atherosclerosis.

When carotid plaque and CCA-IMTs (separately) were added together into the multivariable-adjusted model, only the association between carotid plaque and falls remained significant. The existing literature indicate the presence of carotid plaque is more powerful in detecting cardiovascular risk compared to CCA-IMT [39, 40], while CIMT is a less reliable and precise measure of carotid atherosclerosis as it may also increase due to non-pathological causes [41]. This may partly explain why the associations between CCA-IMTs and falls were attenuated after including prevalent carotid plaque into the multivariable-adjusted model.

Falls have been attributed to a combination of risk factors associated with gait and balance problems as well as visual and cognitive impairments [42]. Carotid plaque, particularly more advanced stenosis, is known to diminish cerebral blood flow [43]. Poor cerebral blood flow leads to syncope, ischaemic stroke and brain infarction resulting in motor, sensory, cognitive, and visual deficit [44], which are all associated with higher falls risk. Of note, Gray and colleagues reported an association between carotid stenosis and higher incidence of self-reported falls after adjustment for cardiovascular risk factors in community dwelling adults with cognitive dysfunction (n=80) [22]. Notably, elevated subclinical cardiovascular biomarkers such hs-cTnT and NT-proBNP are associated with greater falls risk [45]. Transient cardiovascular events and clinical CVD are also associated with falls [46, 47]. As such, screening for the presence of vascular disease may provide an important insight to identify individuals in need of medical optimisation in terms of falls risk or who may benefit from falls prevention interventions. Specifically, regular exercise and healthy dietary habits (e.g., increasing fruit and vegetable intake) would appear to have a benefit in reducing vascular disease and falls [48, 49]. More recent studies have also suggested providing individuals with knowledge of carotid atherosclerosis can reduce cardiovascular risk potentially via improving healthy lifestyle choices [50, 51].

Women with carotid plaque in our study also had 67% greater odds of weak grip strength compared to those without carotid plaque, which is linked towards the pathophysiology of falls [52]. We have also reported in this cohort that AAC, an advanced marker of atherosclerosis, was linked with weaker grip strength but not TUG [11]. Contrary to our findings, others have reported that the presence of carotid plaque is associated with slower TUG [53]. Carotid atherosclerosis is associated with cerebral infraction and stroke [54] which in turn can affect neuromuscular function making it complicated to explain why carotid atherosclerosis is more strongly related with weaker grip strength but not to slower TUG performance in our cohort. Nevertheless, an inverse correlation between CCA-IMT and muscle strength has been previously reported in younger women (n=70, ~21 years) [55]. Of note, in a cross-sectional study of older people (189 hospitalized patients, mean age=79.3 ± 6.9), ankle brachial index a non-invasive measure of subclinical peripheral atherosclerosis has been shown to be associated with subjectively assessed functional status (activities of daily living and instrumental activities of daily living), which are designed to assess fundamental skills typically needed to manage routine tasks, in hospitalised older men and women. However, no association was found between ankle brachial index and falls [56]. Carotid atherosclerosis may influence falls risks acutely through syncope/pre-syncope and possibly also impaired autonomic responses (carotid sinus baroreceptors), whilst low ABI may impair lower limb co-ordination over the long-term as well as impair functional capacity through ischaemic pain as noted in the cited study. Of note, we have also observed a negative but weaker correlation between CCA-IMT (maximum), and grip strength measured two years after the assessment of CCA-IMT.

This study has several strengths including a robust and well characterised cohort of predominantly healthy older Australian women. We had the benefit of a data linkage service meaning this study includes long-term follow-up of fall-related hospitalizations over 11.5 years. Carotid atherosclerosis was assessed using B-mode ultrasound, which is a safe and non-invasive technique that can be performed with a portable machine. IMT at CCA were also determined with repeated measurements to minimise measurement error. However, assessment was not undertaken at the carotid bifurcation and internal arteries. Further, studies with newer carotid ultrasound machines and with measurements undertaken at all carotid artery sites prone to tissue damage are therefore likely to further advance our understanding of the link between carotid atherosclerosis and musculoskeletal health. This study was observational and so we cannot claim causality or exclude the chance of bias due to unmeasured confounding. However, we tried to minimise residual confounding by considering several potential muscle and vascular factors linked to falls. Carotid atherosclerosis was assessed three years after the baseline covariates were assessed which may have affected the strength of the associations. Finally, the findings of this study may not be generalized to other populations.

Conclusions

Measures of carotid atherosclerosis are associated with higher long-term fall-related hospitalization in community-dwelling older women. This work highlights the importance of considering vascular health (e.g., atherosclerosis) when trying to assess an individual's falls risk. Future studies should investigate the utility of various clinical measures of atherosclerosis, which can be used simultaneously to identify individuals at risk of both vascular disease and falls.

Author contributions

AKG, MS, JRL and RLP study concept and design. AKG, MS, and JRL conducted the data analyses. AKG, MS, and JRL drafted the manuscript. JRL, AJR, MS, CPB, and JMH supervised the study. All authors read and approved the final version of the manuscript. AKG, MS and JRL have the primary responsibility for the final content.

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Figure captions

Brief title: Univariate analysis indicating association between carotid plaque and falls

Figure 1: Kaplan-Meier survival curve univariate analysis for the relationship between the presence of carotid plaque and fall-related hospitalization. Carotid plaque present versus absent are represented by grey and black lines, respectively.

Declaration of competing Interests

We have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Baseline characteristics of the participants in 1998 according to presence/absence of focal carotid plaque[a]

	All participants (N=1116)	Focal carotid plaque	
		Absent (n=563)	**Present** (n=553)
Demographics			
Age[b], years	75.1 ± 2.7	**74.9 ± 2.6**	**75.3 ± 2.7**
Calcium treatment group[b], yes (%)	545 (50.0)	288 (52.7)	257 (47.4)
Body mass index (BMI)[c], kg/m^2	27.1 ± 4.9	26.9 ± 4.3	27.3 ± 4.6
Prevalent atherosclerotic vascular disease, yes (%)	122 (10.9)	**40 (7.1)**	**82 (14.8)**
Smoked ever[d], yes (%)	381 (35.1)	**160 (29.4)**	**221 (40.9)**
Prevalent diabetes mellitus[b], yes (%)	59 (5.4)	**19 (3.5)**	**40 (7.4)**
Lipid lowering medications[b], yes (%)	202 (18.5)	**80 (14.6)**	**122 (22.5)**
Blood pressure lowering medication[b], yes (%)	470 (43.2)	**213 (38.9)**	**257 (47.4)**
Physical function			
Physical activity[c], kJ/day	115 (43-204)	111 (45-198)	118 (40-210)
Grip strength[e], kg	20.8 ± 4.6	20.8 ± 4.6	20.7 ± 4.6
Timed-up-and-go[f], sec	9 (8-11)	9 (9-11)	9 (9-11)
Prevalent falls[g], yes (%)	105 (9.6)	52 (9.3)	53 (9.8)
Mean CCA-IMT[h], mm	0.78 ± 0.13	**0.75 ± 0.11**	**0.81 ± 0.14**
Maximum CCA-IMT[h], mm	0.92 ± 0.15	**0.89 ± 0.13**	**0.96 ± 0.17**

Data presented as mean ± SD, median (IQR) or number *n* and (%); Bolded numbers indicate p <0.05 in comparison between carotid plaque absent versus present using independent sample t test, Mann–Whitney *U* test, Chi-square test where appropriate; CCA-IMT: common carotid artery intima-media thickness; [a]The presence of focal carotid plaque was assessed in 2001,[b](n=1089), [c](n=1087), [d](n=1084), [e](n=1107), [f](n=1115), [g](n=1099) and [h](n=1100).

Table 2. Hazard ratios (HR) for injurious fall-related hospitalizations

	Focal carotid plaque (N=1116)		Carotid plaque severity (% stenosis) (N=1116)			Per SD CCA-IMT (N=1100)	
Injurious falls	Absent (n=563)	Present (n=553)	None (n=563)	Less advanced (<25%) (n=391)	Advanced (≥25%) (n=162)	Mean (SD=0.13)	Maximum (SD=0.15)
Event, n (%)	189 (33.6)	239 (43.2)	189 (33.6)	164 (41.9)	75 (46.3)	421 (37.7)	428 (37.7)
Unadjusted	Referent	**1.51 (1.25-1.83)**	Referent	**1.45 (1.18-1.79)**	**1.68 (1.28-2.19)**	**1.13 (1.04-1.23)**	**1.13 (1.04-1.24)**
Minimally-adjusted	Referent	**1.48 (1.22-1.79)**	Referent	**1.41 (1.14-1.75**	**1.64 (1.25-2.15)**	**1.11 (1.01-1.21)**	**1.12 (1.02-1.22)**
Multivariable-adjusted	Referent	**1.44 (1.18-1.76)**	Referent	**1.38 (1.12-1.72)**	**1.61 (1.21-2.13)**	**1.10 (1.00-1.21)**	**1.11 (1.01-1.22)**

Bolded number indicate p <0.05; Minimally-adjusted: age, BMI and treatment; Multivariable-adjusted: minimally-adjusted plus prevalent diabetes, atherosclerotic vascular disease and falls, statin and antihypertensive medication use, and physical activity; CCA-IMT: Common Carotid Artery Intima-Media Thickness.

Table 3. Hazard ratios (HR) for injurious fall-related hospitalization after inclusion of falls risk factors

Covariates	**Injurious falls** *(*HR 95%CI)
Multivariable-adjusted	**1.44 (1.18-1.76)**
+Per SD CCA-IMT, mean	**1.43 (1.16-1.75)**
+ Per SD CCA-IMT, maximum	**1.42 (1.16-1.74)**
+AAC-24 score	**1.34 (1.06-1.68)**
+Grip strength	**1.42 (1.16-1.73)**
+TUG test	**1.44 (1.18-1.76)**
+Grip strength and TUG test	**1.42 (1.16-1.73)**
+25(OH)D vitamin D at baseline	**1.42 (1.15-1.75)**
+ mean SBP and DBP	**1.40 (1.15-1.72)**
+eGFR creatinine	**1.41 (1.14-1.74)**
+ age at menopause	**1.46 (1.20-1.79)**
+dietary calcium intake	**1.47 (1.20-2.79)**

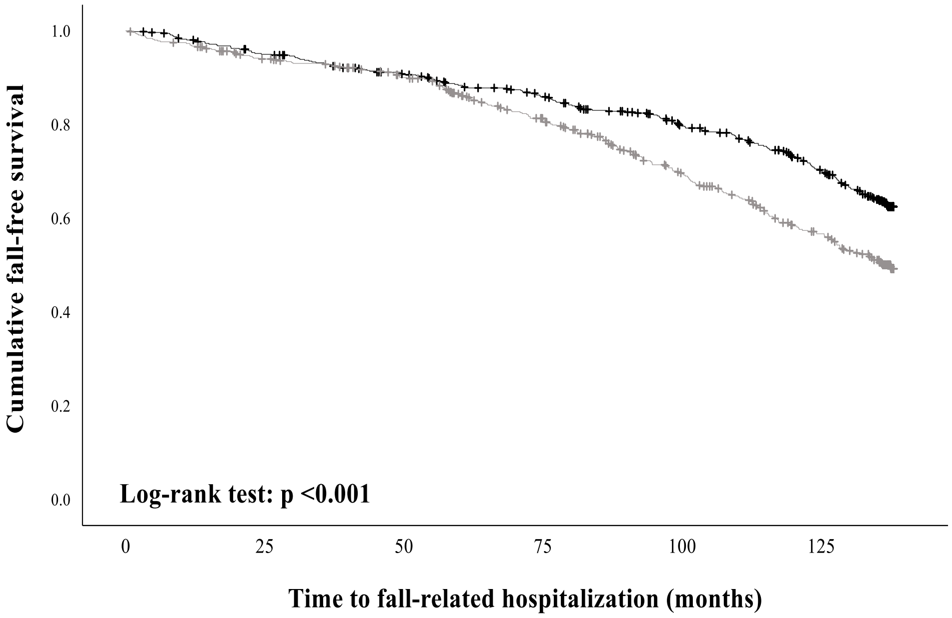
Bolded number indicate $p < 0.05$; Multivariable-adjusted: minimally-adjusted plus prevalent diabetes, atherosclerotic vascular disease and falls, statin and antihypertensive medication use, and physical activity; CCA-IMT: Common Carotid Artery Intima-Media Thickness; AAC-24: Abdominal aortic calcification score-24; TUG test: Timed-up-go test

Table 4. Odds ratios (OR) for weak grip strength and slow TUG

Outcome	Focal carotid plaque (N=1066)		Carotid plaque severity (%stenosis) (N=1066)			Per SD CCA-IMT (N=1050)	
	Absent (n=541)	Present (n=525)	None (n=541)	Less advanced (<25%) (n=370)	Advanced (≥25%) (n=157)	Mean (SD=0.13)	Maximum (SD=0.15)
Grip strength (<22 kg) #							
Events, n (%)	401 (74.1)	424 (80.8)	401 (74.1)	303 (81.9)	125 (78.6)	810 (77.1)	810 (77.1)
Unadjusted	Referent	**1.47 (1.10-1.96)**	Referent	**1.57 (1.13-2.18)**	1.28 (0.84-1.96)	1.12 (0.96-1.30)	**1.17 (1.00-1.37)**
Minimally-adjusted	Referent	**1.48 (1.10-2.00)**	Referent	**1.59 (1.14-2.23)**	1.28 (0.82-1.99)	1.06 (0.91-1.23)	1.11 (0.95-1.30)
Multivariable-adjusted	Referent	**1.67 (1.15-2.41)**	Referent	**1.81 (1.20-2.73)**	1.37 (0.79-2.38)	1.05 (0.88-1.24)	1.10 (0.92-1.31)
TUG test (>10.2 s) ##							
Events, n (%)	279 (51.4)	295 (56.5)	279 (51.4)	202 (55.0)	95 (59.7)	560 (53.3)	560 (53.3)
Unadjusted	Referent	1.23 (0.97-1.57)	Referent	1.16 (0.89-1.51)	1.41 (0.98-2.03)	1.09 (0.96-1.23)	1.09 (0.97-1.23)
Minimally-adjusted	Referent	1.16 (0.90-1.50)	Referent	1.08 (0.82-1.44)	1.38 (0.94-2.02)	1.04 (0.91-1.18)	1.04 (0.91-1.18)
Multivariable-adjusted	Referent	1.15 (0.86-1.54)	Referent	1.09 (0.80-1.50)	1.32 (0.85-2.05)	0.98 (0.85-1.13)	0.96 (0.83-1.11)

Bolded number indicate $p < 0.05$; Minimally-adjusted: age, BMI and treatment; Multivariable-adjusted: minimally-adjusted plus prevalent diabetes, atherosclerotic vascular disease, smoking, statin use, and physical activity, and #grip strength or ##TUG at baseline; CCA-IMT: Common Carotid Artery Intima-Media Thickness.

Figure(s)



Cumulative fall-free survival
1.0
0.8
0.6
0.4
0.2
0.0
Log-rank test: p <0.001
0
25
50
75
100
125
Time to fall-related hospitalization (months)

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