Journal of the American Heart Association

ORIGINAL RESEARCH

Carotid Lumen Diameter Is Associated With All-Cause Mortality in the General Population

Felix Fritze, MD; Stefan Groß, PhD; Till Ittermann, PhD; Henry Völzke, MD; Stephan B. Felix, MD; Ulf Schminke, MD; Marcus Dörr, MD; Martin Bahls, PhD

BACKGROUND: Common carotid intima–media thickness (cIMT) is a biomarker for subclinical atherosclerosis and is associated with all-cause as well as cardiovascular mortality. Higher cIMT is accompanied by a compensatory increase in lumen diameter (LD) of the common carotid arteries. Whether cIMT or LD carry more information with regard to mortality is unclear.

METHODS AND RESULTS: A total of 2751 subjects (median age 53 years; 52% female) were included. During a median follow-up of 14.9 years (range: 12.8–16.5) a total of 506 subjects died. At baseline, cIMT and LD were assessed by carotid ultrasound scans. Multivariable Cox regression models were used to relate cIMT, LD, LD adjusted for cIMT (LD+cIMT), and LD/cIMT ratio with all-cause, cardiovascular, and noncardiovascular mortality. All models were ranked using Akaike's information criterion. Harrel's c statistic was used to compare the models' predictive power for mortality. A 1-mm increase in LD was related to a higher risk for all-cause mortality (hazard ratio [HR], 1.29; 95% CI, 1.14–1.45, $P<0.01$). This association remained significant when cIMT was added to the model (HR, 1.26; 95% CI, 1.11–1.42; $P<0.01$). A 1-mm higher cIMT was also related with greater mortality risk (HR, 1.73; 95% CI, 1.09–2.75). The LD/cIMT ratio was not associated with all-cause mortality. LD had the lowest Akaike's information criterion regarding all-cause mortality and improved all-cause mortality prediction compared with the null model ($P=0.01$). CIMT weakened all-cause mortality prediction compared with the LD model.

CONCLUSIONS: LD provided more information for all-cause mortality compared with cIMT in a large population-based sample.

Key Words: cardiovascular disease ■ cardiovascular mortality ■ carotid lumen diameter

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity in Western civilizations.[1,2] Carotid intima–media thickness (cIMT) is a useful noninvasive biomarker for cardiovascular risk assessment and is significantly related to future CVD event risk. An increased cIMT is related to a higher risk for coronary heart disease (CHD) and stroke.[3] Overall, cIMT has been proposed as a marker for cardiovascular risk assessment in representing the patient's systemic atherosclerotic disease burden.[4-6] Results of the CAPS (Carotid Atherosclerosis Progression Study) raised concerns regarding the use of cIMT as a viable marker for individual cardiovascular risk stratification in the general population.[7] Recently, larger meta-analyses came to different conclusions on cIMT's prognostic significance, with some doubting the reliability altogether,[8] and some calling the different methodology of the numerous studies into question.[9]

The lumen of the coronary arteries distends overproportionally during early stages of atherosclerosis.[10] Similar effects were observed for the carotid arteries.[11-13] Increased carotid lumen diameters (LD) have also been independently related to numerous cardiovascular risk factors.[12,14-16] Accordingly, carotid distension has been associated with incident cardiovascular events.[3,17] Furthermore, a recent meta-analysis of data

Correspondence to: Martin Bahls, PhD, Department of Internal Medicine B, University Medicine Greifswald, Ferdinand-Sauerbruch-Str, Greifswald 17475, Germany. E-mail: martin.bahls@uni-greifswald.de

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015630

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In clinical practice carotid intima–media thickness is used for individualized cardiovascular risk assessment.

What Are the Clinical Implications?

- Our results support the notion that the more easily obtainable lumen diameter may be a better predictor for cardiovascular and all-cause mortality; thus, this measure is potentially preferable over the current standard.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
CCA	common carotid artery
CHD	coronary heart disease
cIMT	carotid intima–media thickness
CVD	cardiovascular disease
HR	hazard ratio
LD	lumen diameter
SHIP	Study of Health in Pomerania

from 4 larger studies found that LD was associated with a higher risk of any cardiovascular event and mortality, despite adjusting for other carotid parameters such as arterial stiffness and pulse wave velocity.[18] Even though this large meta-analysis with 4887 participants reported that LD was associated with a higher risk for mortality, substantial heterogeneity was found between studies (I^2 79%–86%, depending on model adjustment). Furthermore, once adjusted for cIMT, the association became nonsignificant. To the best of our knowledge no study has yet compared the informative value of cIMT and LD with regard to their association with mortality.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Forschungsverbund Community Medicine at community-medicine@uni-greifswald.de.

Study Population

This study is based on data of the first follow-up of the population-based cohort SHIP (Study of Health in Pomerania), which was conducted from 2002 to 2006 in northeastern Germany. For the baseline examination, a total of 7008 subjects between the ages of 20 and 79 years were randomly selected in twelve 5-year strata from the 212 157 inhabitants of this area. Of those invited, 4308 subjects agreed to participate in the comprehensive baseline examination (response: 68.8%) between 1997 and 2001. After 5 years the participants were invited for the first follow-up (SHIP-1). A total of 3300 subjects were interviewed and examined (response 83.6%). The 10- and 15-year follow-up studies are named SHIP-2 and –3, respectively. The baseline for this analysis was SHIP-1. Further details on the study protocol of SHIP as well as information on the interviews, and medical and laboratory examinations have been published elsewhere.[19,20] The study was approved by the ethics committee of the University of Greifswald, complies with the Declaration of Helsinki, and all study participants gave written informed consent. A flow chart with information on inclusion and exclusion of study participants is provided in Figure 1.

Interview, Medical and Laboratory Examination

Data were collected with respect to the participant's socioeconomic characteristics (net income, level of education), behavioral risk factors (smoking status, daily alcohol intake), and health status using standardized computer-assisted personal interviews and questionnaires. All medical examinations were performed by certified personnel and standardized

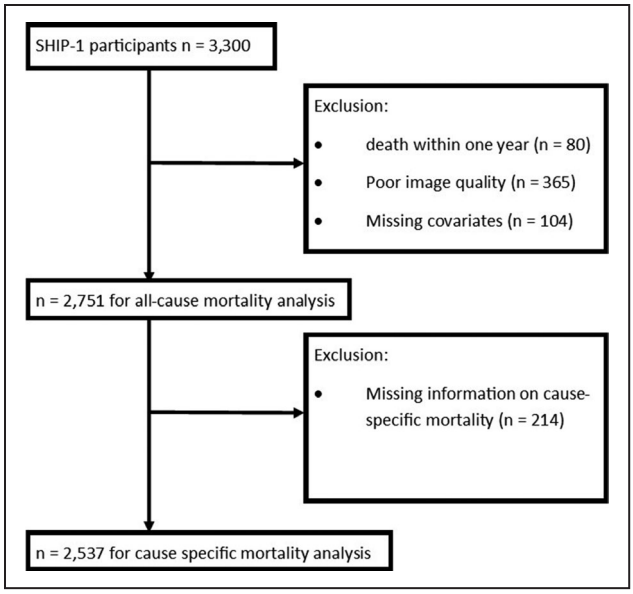

Figure 1. Flowchart detailing information on inclusion and exclusion criteria.
SHIP indicates Study of Health in Pomerania.

laboratory measurements. Low-density lipoprotein cholesterol was measured by lipoprotein electrophoresis (HELENA SAS-3 system; Helena 7 BioSciences Europe, Tyne & Wear, UK). Total cholesterol and serum creatinine levels (modified kinetic Jaffé method) were determined with a Siemens Dimension RxL (Siemens Healthcare Diagnostics, Eschborn, Germany). Height and weight of the subjects were measured. Body mass index (BMI) was calculated by dividing body height (m) by body mass (kg) squared. Medication was assessed based on the anatomic, therapeutic, and chemical code.

Vital status information of study participants was regularly collected from population registries. Participants were censored at loss to follow-up. Death certificates were requested from the local health authorities and were coded by certified nosologists according to the *International Classification of Diseases, 10th Revision* (*ICD-10*). Two internists independently validated the underlying cause of death and performed a joint reading together with a third internist in cases of disagreement.

Carotid Ultrasonography

The carotid ultrasonography was conducted for each subject using the Diasonics VST-Gateway (Santa Clara, CA) equipped with a 5-MHz linear array transducer with an axial resolution <0.5 mm. Scans from the distal straight portion of both common carotid arteries (CCA) were recorded and digitally stored by experienced and certified examiners. Ten IMT measurements were taken in 1-mm steps at the far wall of the most distal straight portion of each CCA proximally from the bifurcation. Mean far-wall CCA-IMT was calculated as the arithmetic mean of all measurements from both sides. All measurements of intra-reader, intra-observer, inter-reader, and inter-observer agreements revealed mean differences ±2 SD of <5±<25%.

LD was defined as the distance between lagging edge near-wall intima-to-lumen interface to leading edge far-wall lumen-to-intima interface. LD was measured manually at 3 different measurement points within the first 12.4 mm proximal from the carotid bulb. For all study participants, a total of at least 3 separate images of the left and right carotid artery were used. Thus, the LD for each subject was calculated by averaging a total of at least 6 images with 3 measurements each. In case of carotid stenosis, no LD measurement was performed. A single reader was trained on 200 images until the intraclass correlation was >0.9. The SD between measurements for the right and left outer diameter was 0.19 (95% CI, 0.195–0.202) mm and 0.19 (95% CI, 0.192–0.201) mm, respectively. The intraclass correlation for the outer diameter was 0.95 (95% CI, 0.952–0.957) for the right and 0.94 (95% CI, 0.942–0.948) for the left side. The SD for the LD was 0.21 (95% CI, 0.203–0.211) mm on the right and 0.211 (95% CI, 0.207–0.215) mm on the left side. The intraclass correlation was 0.933 (95% CI, 0.930–0.937) on the right and 0.914 (95% CI, 0.909–0.918) on the left side.

Carotid plaques were qualitatively defined as any focal thickening of the intima–media complex protruding into the vessel lumen or as a focal increase of echogenicity with a homogeneously hyperechoic echotexture within an otherwise hypoechoic intima–media complex. The presence of carotid plaques was defined as the appearance of at least 1 plaque in one of the following arterial segments: CCA, carotid bulb (ie, the segment between first CCA enlargement and flow divider), and internal and external carotid arteries of both sides.

After exclusions because of poor image quality (n=365; 11%), death within 1 year after ultrasonography (excluded to account for underlying occult disease[21]; n=80; 2%) and missing data (n=104; 3%), 2751 subjects including 506 deaths were used for all-cause mortality analysis. Follow-up time was 12.76 to 16.44 years (median 14.68 years, 37 770 person-years). A total of 214 subjects had to be excluded from cause-specific analysis because of insufficient information on cause of death, resulting in n=2537 subjects including 292 deaths (113 cardiovascular deaths) for those analyses (Figure 1).

Statistical Analysis

A total of 4 multivariable Cox regression models based on cIMT, LD, LD with adjustment for cIMT (LD+cIMT), and LD/cIMT ratio were used with the Efron method for ties. The models tested a possible association with all-cause, CV, and noncardiovascular mortality. Cardiovascular and noncardiovascular mortality were modeled as competing risks. Cardiovascular mortality was defined using the *ICD-10* codes I10–I79, therefore containing stroke, CHD, and numerous other related conditions. Necessary confounders were identified using a directed acyclic graph.[22] Accordingly, all Cox regression models were adjusted for age, sex, current smoking, present diabetes mellitus, hypertension, daily alcohol intake, BMI, total cholesterol/high-density lipoprotein cholesterol ratio, level of education, and income.

Proportional hazards models were used to identify the association between cIMT, LD, LD and cIMT, and the LD/cIMT ratio with incident coronary artery disease and coronary heart disease. Five different models were assessed:

Model 1: age and sex.
Model 2: model 1+systolic blood pressure.

Model 3: model 2+current smoking+diabetes mellitus+high-density lipoprotein/total cholesterol ratio+BMI+triglycerides.
Model 4: model 3+lipid-lowering medication+antihypertensive medication.
Model 5: model 4+plaque.

The 4 multivariable Cox regression models (LD, cIMT, LD+cIMT, LD/cIMT ratio) plus a null model (containing only the set of confounders) were ranked using Akaike's information criterion (AIC) to test whether cIMT or LD better explain the association with mortality.[23] Likelihood and loss of information were represented in the calculated AIC for each model, which were ranked based on the difference in AIC (ΔAIC) between the model with the smallest AIC and AIC of a particular other model (AIC_i). The model with the lowest AIC was considered to have the highest support explaining mortality data. When using AIC, models with ΔAIC ≤2 are considered to have substantial support of having the highest explanatory value. Models within a $4 \leq \Delta AIC_i \leq 7$ range are considered to have some support, but considerably less than models with ΔAIC ≤2. Models with $\Delta AIC_i > 10$ have essentially no support. Akaike weights were calculated to provide the probability in percent of a model being the model with the highest support. Additionally, evidence ratios provide information on how more likely the model with minimum AIC is in relation to the respective model.[23]

In a third step, Harrel's c statistic was used to quantify the discriminatory value between the different models.[24] Models containing LD, cIMT, LD+cIMT, and LD/cIMT ratio were compared with the null model with regard to their association between all-cause, cardiovascular, and noncardiovascular mortality, respectively. In addition, the cIMT, LD+cIMT, and LD/cIMT ratio models were tested against the LD model in the same way.

In an attempt to find potential differences between cIMT and LD with regard to established cardiovascular risk factors and comorbidities, we calculated age and sex adjusted regression models between both parameters and smoking, hypertension, type 2 diabetes mellitus, BMI, low-density lipoprotein cholesterol, as well as waist circumference.

Since atherosclerotic plaques are a sign of overt and manifest CVD, we performed a sensitivity analysis that included a plaque score. This score was the sum of the plaques present at left or right external carotid artery, common carotid artery, internal carotid artery, and bifurcation. Thus, individuals without any plaque scored zero and study participants with plaque on all 4 locations scored a 4. Further sensitivity analyses were performed by excluding subjects with chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), type 2 diabetes mellitus (defined as HbA1c >6.5%) or antidiabetic medication (anatomic-therapeutic-chemical code A10) as well as prior stroke or myocardial infarction. All analysis was conducted using STATA 15.1 (StataCorp LLC, College Station, TX).

RESULTS

Study Population

Among the 2751 subjects, 506 deaths occurred within follow-up, leaving 2245 survivors. Compared with the nonsurvivors, the group of survivors had more females (56.35% versus 34.58%), fewer hypertensive subjects (49.62% versus 84.98%), and fewer subjects with diabetes mellitus (7.71% versus 29.05%). The proportion of current smokers was similar in both groups (survivors 27.13%, nonsurvivors: 21.34%). Concerning education and income, the proportion of nonsurvivors was higher in the lower strata, respectively.

The mean carotid LD was 6.17 mm (SD 0.7) for the survivors and 6.85 mm (SD 0.4) for the nonsurvivors. Mean maximum cIMT was 0.78 mm (SD 0.15) for the survivors and 0.95 mm (SD 0.21) for the nonsurvivors. More detailed baseline characteristics of the study population are provided in Table 1 and Table S1.

In 286 subjects, atherosclerotic plaque was present in the CCA. Furthermore, 1526 individuals had plaques at the bifurcation, while 952 and 670 study participants had plaques in the internal carotid artery and external carotid artery, respectively. Information about the study participant characteristics can be found in Table 2.

Correlation Analysis

Current smoking was related to significantly larger LDs (smokers: 6.37; 95% CI, 6.33–6.42 mm versus nonsmokers: 6.26; 95% CI, 6.23–6.29 mm; $P<0.01$) and cIMTs (smokers: 0.825; 95% CI, 0.814–0.835 mm versus nonsmokers: 0.807; 95% CI, 0.800–0.813 mm; $P<0.01$). Hypertension was also associated with a larger LD (normotensive: 6.19; 95% CI, 6.15–6.23 mm versus hypertensive: 6.38; 95% CI, 6.34–6.41 mm; $P<0.01$) and cIMT (normotensive: 0.799; 95% CI, 0.790–0.807 mm; $P<0.01$). Individuals with diabetes mellitus also had greater LDs (no diabetes mellitus, 6.27; 95% CI, 6.24–6.29 mm versus diabetes mellitus, 6.50; 95% CI, 6.43–6.57 mm; $P<0.01$) as well cIMTs (no diabetes mellitus: 0.808; 95% CI, 0.803–0.814 mm versus diabetes mellitus: 0.832; 95% CI, 0.816–0.848 mm; $P<0.01$). A 1 kg/m^2 increase in BMI was related to a larger LD (coefficient [β] 0.022; 95% CI, 0.017–0.027; $P<0.01$) and cIMT (β 0.002; 95% CI, 0.001–0.003; $P<0.01$), respectively. A 1- cm larger waist circumference was also associated with a greater LD (β 0.011; 95% CI, 0.009–0.013; $P<0.01$) and cIMT (β 0.0007; 95% CI, 0.0003–0.0012; $P<0.01$).

Table 1. Description of the Study Population

Parameter	Survivors	Nonsurvivors	Total
N (%)	2245 (81.61)	506 (18.39)	2751
Cardiovascular death, n (%)	…	113 (22.33)	113 (4.1)
Noncardiovascular deaths, n (%)		179 (35.38)	179 (6.51)
Female n (%)	1265 (56.36)	175 (34.58)	1440 (52.34)
Age, y (SD)	49.78 (13.33)	69.29 (10.81)	53.37 (14.95)
BMI, kg/m^2 (SD)	27.46 (4.7)	29.15 (4.9)	27.77 (4.77)
Waist circumference, cm (SD)	90.61 (13.55)	99.12 (12.87)	92.17 (13.82)
MetS, n (%)	780 (36.76)	297 (61.75)	1077 (41.38)
Total cholesterol/HDL-C ratio (SD)	0.63 (0.08)	0.64 (0.08)	0.63 (0.08)
Current smoking, n (%)	609 (27.13)	108 (21.34)	717 (26.06)
Alcohol intake, last 30 d, g/d (SD)	9.36 (13.33)	8.09 (13.35)	9.13 (14.01)
LDL-C, mmol/L (SD)	3.54 (1.01)	3.45 (0.96)	3.52 (1.00)
COPD, n (%)	152 (6.77)	79 (15.61)	231 (8.40)
Gout, n (%)	124 (5.59)	61 (12.2)	185 (6.81)
Atrial fibrillation, n (%)	16 (0.72)	30 (6.12)	46 (1.69)
CRP, mg/dL (SD)	1.85 (1.84)	2.64 (2.15)	1.96 (1.91)
eGFR, mL/min (SD)	99.03 (16.04)	81.89 (19.8)	95.93 (18.03)
Blood glucose, mmol/L (SD)	5.53 (1.16)	6.30 (2.1)	5.67 (1.41)
Systolic BP, mm Hg (SD)	130.05 (18.65)	140.52 (21.22)	131.97 (19.57)
Diastolic BP, mm Hg (SD)	81.76 (10.13)	79.66 (11.72)	81.37 (10.47)
Medications			
Antidiabetic agents (ATC A10), n (%)	113 (5.03)	101 (19.96)	214 (7.78)
Antithrombotic agents (ATC B01), n (%)	225 (10.02)	206 (40.71)	431 (15.67)
Cardiac agents (ATC C01), n (%)	88 (3.92)	140 (27.67)	228 (8.29)
Antihypertensive agents (ATC C02), n (%)	24 (1.07)	16 (3.16)	40 (1.45)
Diuretics (ATC C03), n (%)	88 (3.92)	115 (22.73)	203 (7.38)
Peripheral vasodilators (ATC C04), n (%)	11 (0.49)	21 (4.15)	32 (1.16)
β-Blocker (ATC C07), n (%)	454 (20.22)	216 (42.69)	670 (24.35)
Calcium channel blockers (ATC C08), n (%)	123 (5.48)	114 (22.53)	237 (8.62)
Cardio-spec. calcium channel blockers (ATC C08d), n (%)	16 (0.71)	23 (4.55)	39 (1.42)
RAAS modulators (ATC C09), n (%)	401 (17.86)	258 (50.99)	659 (23.95)
Lipid-lowering medication (ATC C10), n (%)	234 (10.42)	138 (27.27)	372 (13.52)
Bronchodilators (ATC R03), n (%)	83 (3.7)	60 (11.86)	143 (5.20)

ATC indicates anatomic, therapeutic, and chemical classification; BMI, body mass index; BP, blood pressure; Cardio-spec, cardio-specific; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; and RAAS, renin-angiotensin system.

Only 1 cardiovascular risk factor showed opposite relations between LD and cIMT. Specifically, a 1 mmol/L low-density lipoprotein cholesterol higher concentration was associated with a smaller LD (β −0.03; 95% CI, −0.06 to −0.01; *P*<0.01) but a larger cIMT (β 0.008; 95% CI, 0.004–0.014; *P*<0.01).

Cox Regression Models for the Mortality Analysis

The results for all Cox regression models are shown in Figure 2. The survival curve for the relationship between LD and all-cause mortality is shown in Figure 3. LD was positively associated with a higher risk for all-cause mortality (hazard ratio [HR] 1.29 per mm increase; 95% CI, 1.14–1.45; *P*<0.01). When cIMT was added, this relation remained significant (LD+IMT: HR, 1.26 per mm increase; 95% CI, 1.11–1.42; *P*<0.01). A 1-mm increase in cIMT (HR, 1.73; 95% CI, 1.01–2.75; *P*=0.02) was also related to all-cause mortality. The LD/cIMT ratio (HR, 1.02; 95% CI, 0.95–1.1; *P*=0.54) was not associated with all-cause mortality.

Likewise, LD was positively associated with a higher risk for cardiovascular mortality (HR, 1.29 per mm increase; 95% CI, 1.01–1.64; *P*=0.04). This relation

Table 2. Descriptive Population Characteristics Stratified by Plaque Score Provided as Means and SD for Continuous Variables and n % for Dichotomic Parameters

Parameters	No Plaque	1 Plaque	2 Plaques	3 Plaques	4 Plaques
N	1158	563	399	451	180
All-cause mortality, n (%)	42 (3.63)	86 (15.28)	93 (23.31)	180 (39.91)	105 (58.33)
Female, n (%)	680 (58.72)	321 (57.02)	184 (46.12)	193 (42.79)	62 (34.44)
Age, y (SD)	41.73 (10.74)	56.44 (10.90)	61.94 (10.61)	65.09 (10.34)	70.29 (9.59)
Hypertension, n (%)	367 (31.69)	353 (62.70)	298 (74.69)	363 (80.49)	163 (90.56)
Systolic BP, mm Hg (SD)	124.61 (16.97)	133.86 (18.16)	138.97 (18.74)	138.34 (20.31)	141.93 (22.30)
Diastolic BP, mm Hg (SD)	80.66 (9.81)	82.80 (9.84)	83.43 (10.61)	81.00 (11.24)	77.65 (12.58)
Current smoking, n (%)	381 (32.90)	134 (23.80)	80 (20.05)	85 (18.85)	37 (20.56)
Diabetes mellitus, n (%)	31 (2.68)	62 (11.01)	58 (14.54)	111 (24.61)	58 (32.22)
BMI, kg/m^2 (SD)	26.23 (4.44)	28.47 (4.67)	29.20 (4.69)	29.39 (4.82)	28.29 (4.38)
Alcohol intake, last 30 d, g/d (SD)	9.70 (14.13)	8.87 (13.07)	9.46 (15.76)	8.18 (13.11)	7.86 (14.08)
TG, mmol/L (SD)	1.60 (1.99)	1.88 (1.31)	1.92 (1.18)	2.05 (1.53)	2.00 (1.90)
Cholesterin, mmol/L (SD)	5.33 (1.10)	5.74 (1.20)	5.74 (1.10)	5.66 (1.26)	5.49 (1.17)
HDL-C, mmol/L (SD)	1.25 (0.42)	1.17 (0.41)	1.17 (0.46)	1.10 (0.41)	1.06 (0.34)
LDL-C, mmol/L (SD)	3.31 (0.97)	3.72 (1.05)	3.71 (0.92)	3.64 (1.00)	3.55 (1.01)
Total cholesterol/HDL-C ratio (SD)	0.62 (0.09)	0.64 (0.08)	0.64 (0.71)	0.64 (0.08)	0.64 (0.08)
Creatinine, µmol/L (SD)	67.16 (13.96)	68.84 (15.33)	71.37 (17.89)	73.80 (24.21)	87.41 (90.56)
eGFR, mL/min (SD)	105.23 (14.68)	93.59 (15.50)	89.65 (15.32)	86.20 (17.19)	80.53 (21.32)
CRP, mg/dL (SD)	1.70 (1.75)	2.04 (1.94)	2.01 (1.93)	2.29 (2.03)	2.43 (2.20)
Blood glucose, mmol/L (SD)	5.29 (0.71)	5.75 (1.53)	5.86 (1.51)	6.12 (1.83)	6.38 (2.08)
Waist circumference, cm (SD)	86.47 (12.81)	93.80 (12.43)	97.57 (13.68)	98.08 (13.05)	97.02 (12.23)
Ultrasound parameters					
Mean carotid LD, mm (SD)	5.99 (0.58)	6.22 (0.69)	6.49 (0.77)	6.68 (0.80)	7.12 (0.96)
Mean max. IMT, mm (SD)	0.72 (0.98)	0.80 (0.13)	0.86 (0.15)	0.91 (0.17)	1.08 (0.24)
Mean LD/cIMT ratio, (SD)	8.48 (1.13)	7.87 (1.22)	7.71 (1.27)	7.52 (1.38)	6.80 (1.39)
Mean AD, mm (SD)	10.00 (0.66)	7.48 (0.78)	7.82 (0.85)	8.09 (0.87)	8.66 (1.03)
Income					
<500 EUR, n (%)	26 (2.25)	7 (1.24)	6 (1.50)	14 (3.10)	2 (1.11)
500 to <900 EUR, n (%)	105 (9.07)	53 (9.41)	39 (9.77)	51 (11.31)	21 (11.67)
900 to <1300 EUR, n (%)	149 (12.87)	93 (16.52)	75 (18.80)	96 (21.29)	54 (30.00)
1300 to <1800 EUR, n (%)	234 (20.21)	145 (25.75)	113 (28.32)	148 (32.82)	43 (23.89)
1800 to <2300 EUR, n (%)	240 (20.73)	117 (20.78)	83 (20.80)	69 (15.30)	40 (22.22)
2300 to <2800 EUR, n (%)	170 (14.68)	65 (11.55)	38 (9.52)	35 (7.76)	13 (7.22)
2800 to <3300 EUR, n (%)	108 (9.33)	39 (6.93)	23 (5.76)	20 (4.43)	4 (2.22)
≥3300 EUR, n (%)	126 (10.88)	44 (7.82)	22 (5.51)	18 (3.99)	3 (1.67)
Level of education					
No degree, n (%)	3 (0.26)	10 (1.78)	9 (2.26)	21 (4.66)	6 (3.33)
8/9 y of school, n (%)	152 (13.13)	217 (38.54)	213 (53.38)	256 (56.76)	131 (72.78)
10 y of school, n (%)	750 (64.77)	229 (40.67)	118 (29.57)	114 (25.28)	26 (14.44)
High school, college, or university, n (%)	253 (21.85)	107 (19.01)	59 (14.79)	60 (13.30)	17 (9.44)
MetS, n (%)	258 (23.58)	254 (48.11)	206 (53.51)	248 (57.94)	111 (66.07)
COPD, n (%)	79 (6.82)	29 (5.15)	36 (9.02)	61 (13.63)	26 (14.44)
Gout, n (%)	27 (2.35)	43 (7.73)	39 (9.90)	54 (12.22)	22 (12.43)
Atrial fibrillation, n (%)	4 (0.35)	6 (1.07)	10 (2.54)	19 (4.30)	7 (4.05)
Medications					
Antidiabetic agents (ATC A10), n (%)	17 (1.47)	40 (7.10)	41 (10.28)	74 (16.41)	42 (23.33)
Antithrombotic agents (ATC B01), n (%)	37 (3.20)	74 (13.14)	84 (21.05)	158 (35.03)	78 (43.33)

(*Continued*)

Table 2. Continued

Parameters	No Plaque	1 Plaque	2 Plaques	3 Plaques	4 Plaques
Cardiac agents (ATC C01), n (%)	38 (3.28)	80 (14.21)	69 (17.29)	121 (26.83)	64 (35.56)
Antihypertensive agents (ATC C02), n (%)	7 (0.60)	5 (0.89)	8 (2.01)	14 (3.10)	6 (3.33)
Diuretics (ATC C03), n (%)	15 (1.30)	33 (5.86)	30 (7.52)	80 (17.74)	45 (25.00)
Peripheral vasodilators (ATC C04), n (%)	4 (0.35)	4 (0.71)	5 (1.25)	11 (2.44)	8 (4.44)
β-Blocker (ATC C07), n (%)	114 (9.84)	152 (27.00)	130 (32.58)	189 (41.91)	85 (47.22)
Calcium channel blockers (ATC C08), n (%)	16 (1.38)	48 (8.53)	46 (11.53)	78 (17.29)	49 (27.22)
Cardio-spec. calcium channel blockers (ATC C08d), n (%)	2 (0.17)	6 (1.07)	6 (1.50)	13 (2.88)	12 (6.67)
RAAS modulators (ATC C09), n (%)	76 (6.56)	135 (23.98)	138 (34.59)	203 (45.01)	107 (59.44)
Lipid-lowering medication (ATC C10), n (%)	38 (3.28)	80 (14.21)	69 (17.29)	121 (26.83)	64 (35.56)
Bronchodilators (ATC R03), n (%)	43 (3.71)	17 (3.02)	17 (4.26)	46 (10.20)	20 (11.11)
Atherosclerotic plaques					
CCA, n (%)	0 (0)	4 (0.7)	31 (7.77)	71 (15.74)	180 (100)
BIF, n (%)	0 (0)	504 (89.52)	392 (98.25)	450 (99.78)	180 (100)
ACI, n (%)	0 (0)	36 (6.39)	297 (74.44)	439 (97.34)	180 (100)
ACE, n (%)	0 (0)	19 (3.37)	78 (19.55)	393 (87.14)	180 (100)

ACE indicates external carotid artery; ACI, internal carotid artery; AD, external carotid diameter; ATC, anatomic-therapeutic-chemical classification code; BIF, bifurcation; BMI, body mass index; BP, blood pressure; Cardio-spec, cardio-specific; CCA, common carotid artery; cIMT, carotid intima–media thickness; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; EUR, euros; HDL-C, high-density lipoprotein cholesterol; LD, lumen diameter; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; RAAS, renin-angiotensin-aldosterone system; and TG, total triglycerides.

lost significance when cIMT was added to the model (LD+IMT: HR, 1.29 per mm increase; 95% CI, 0.98–1.69; *P*=0.07) (Figure 2). cIMT (HR, 1.42 per mm increase; 95% CI, 0.48–4.25; *P*=0.52) and LD/cIMT ratio (HR, 1.12; 95% CI, 0.94–1.33; *P*=0.20) were not related to cardiovascular mortality.

LD (HR 1.30 per mm increase; 95% CI, 1.08–1.55; *P*<0.01) and cIMT (HR 3.09 per mm increase; 95% CI, 1.37–6.96; *P*<0.01) were positively associated with noncardiovascular mortality. No significant relation with noncardiovascular mortality was found for LD+cIMT (HR per mm increase 1.21; 95% CI, 1.0–1.47; *P*=0.05) and LD/cIMT ratio (HR, 0.96; 95% CI, 0.85–1.08; *P*=0.48).

AIC Ranking for the Mortality Analysis

The detailed results are provided in Table 3. Briefly, the LD model had the lowest AIC regarding all-cause and cardiovascular mortality. For noncardiovascular mortality, the model with lowest AIC included LD and cIMT. For all-cause mortality, in addition to LD only the LD+cIMT (ΔAIC=2.00) model was within the threshold of $\Delta AIC_i \leq 2$. However, the probability of LD being the model with the highest support is greater according to Akaike weights and evidence ratios. With regard to cardiovascular mortality, all models were below the ΔAIC_i of 4. AIC ranking for noncardiovascular mortality showed that the model containing LD and cIMT, LD, or cIMT had ΔAICs <4.

Harrel's c for the Mortality Analysis

The model containing LD provided more information with regard to all-cause mortality compared with the null model (Table 4). Including cIMT reduced the information compared with LD for all-cause mortality. The other relations regarding the prediction of all-cause, cardiovascular, and noncardiovascular mortality are listed in Table 4.

Proportional Hazards Regression Models for Incident CVD and CHD

The results of this analysis are presented in Table 5. Of a total of 1399 individuals, 253 developed CHD during a median follow-up of 10.34 years (range, 4.18–12.94 years). In the age- and sex-adjusted model, LD (HR 1.20 per mm increase; 95% CI, 1.01–1.52; *P*=0.05) was positively associated with incident CHD. LD+cIMT had a significant positive relation with incident CHD in the age and sex (HR 1.27 per mm increase; 95% CI, 1.01–1.60, *P*=0.04) as well as the model adjusted for age, sex, and systolic blood pressure (HR 1.26 per mm increase; 95% CI, 1.00–1.59, *P*=0.05).

During a median follow-up time of 10.35 years (range, 4.18–12.94) 285 study participants (1035 total) developed CVD. The LD+cIMT model adjusted for age and sex was significantly positive associated with incident CVD (HR 1.24 per mm increase; 95% CI,

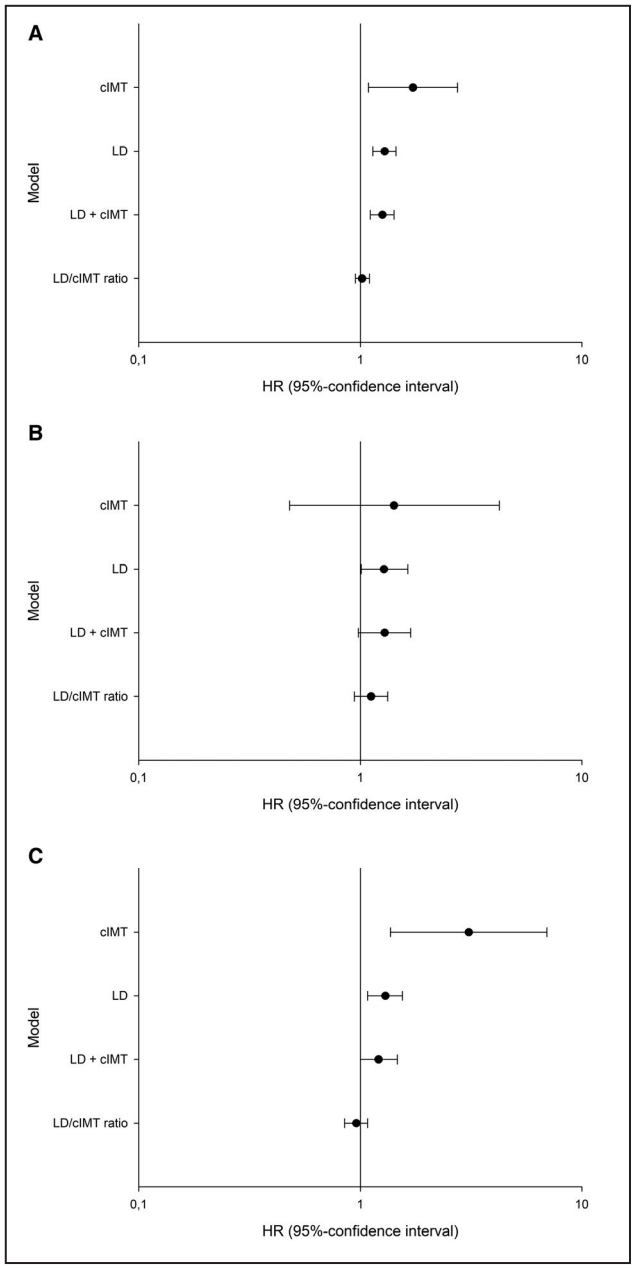

Figure 2. Forest plot with the 4 tested models for (A) all-cause mortality, (B) cardiovascular mortality, and (C) noncardiovascular disease mortality.
2Risk of all-cause mortality caused by increased cIMT, LD, LD+cIMT, and the LD/IMT ratio. HRs for all-cause mortality are reported with 95% CIs for a 1-unit increase adjusting for all other variables in the model. cIMT indicates carotid intima–media thickness; HR, hazard ratio; and LD, lumen diameter.

1.00–1.53, *P*=0.04). The LD/cIMT ratio was positively related to the development of CVD in the fully adjusted mode (HR, 1.11, 95% CI, 1.00–1.23, *P*=0.05).

AIC Ranking for Incident CVD and CHD

The detailed results are provided in Table 6. Briefly, the LD and LD/cIMT models were consistently ranked as

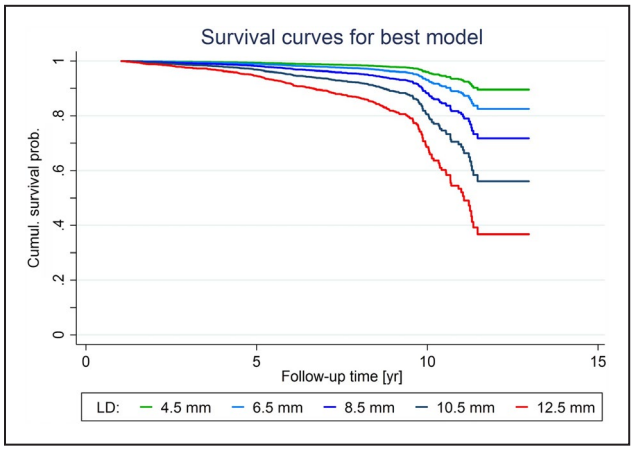

Figure 3. Survival curve of the relationship between LD and all-cause mortality.
LD indicates lumen diameter.

models with the highest predictive value for incident CHD and CVD.

Sensitivity Analyses

The presence of plaque in any of the carotid arteries or at the bifurcation on either side was not associated with all-cause (HR, 1.23, 95% CI; 0.89–1.71) and noncardiovascular mortality (HR, 1.10; 95% CI, 0.67–1.80). Atherosclerotic plaques were related to an increased risk for cardiovascular mortality (HR, 8.47; 95% CI, 1.11–64.58) but not noncardiovascular mortality (HR, 1.10; 95% CI, 0.67–1.80). Additional adjustment for the presence of plaques did not substantially change the associations between LD (HR, 1.28 for each mm increase, 95% CI, 1.14–1.44, *P*<0.01), cIMT (HR, 1.69 for each mm increase; 95% CI, 1.07–2.70, *P*=0.03), LD+cIMT (HR, 1.25 for each mm increase; 95% CI, 1.11–1.42, *P*<0.01) and LD/cIMT (HR, 1.02; 95% CI, 0.95–1.10, *P*=0.14) with all-cause mortality. The relationship between LD (HR per 1 mm increase 1.24; 95% CI, 0.98–1.58), cIMT (HR per 1 mm increase 1.32; 95% CI, 0.45–3.94), LD+cIMT (HR per 1 mm increase 1.25; 95% CI, 0.95–1.64), and LD/cIMT (HR, 1.12; 95% CI, 0.94–1.33) with CV mortality not influenced by additional adjustment for the presence of plaques. Similarly, all parameters but the LD/cIMT ratio were significantly associated with noncardiovascular mortality after adjustment for plaques (LD HR per 1 mm increase 1.30; 95% CI, 1.08–1.55; cIMT HR per 1 mm increase 3.08; 95% CI, 1.36–6.97; LD+cIMT HR, 1.21; 95% CI, 1.00–1.47; LD/cIMT HR, 0.96; 95% CI, 0.85–1.08).

When individuals with chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2) were excluded, the association between LD (HR, 1.31; 95% CI, 1.15–1.49) and LD+cIMT (HR, 1.30;

Table 3. AIC Ranks for the 4 Tested Models Plus the Null Model (Set of Confounders Only)

Rank	Model	Parameters	ΔAIC	AW (%)	ER
All-cause mortality					
#1	LD	19	0.00	55.64	
#2	LD+cIMT	20	0.46	44.22	1.26
#3	cIMT	19	12.32	0.12	472.46
#4	Null model	18	15.9	0.02	2841.67
#5	LD/cIMT ratio	19	17.52	0.01	6360.18
Cardiovascular mortality					
#1	LD	19	0.00	47.07	
#2	LD+cIMT	20	2.0	17.33	2.72
#3	LD/cIMT ratio	19	2.29	14.99	3.14
#4	Null model	18	2.4	14.20	3.32
#5	cIMT	19	3.99	6.42	7.34
Noncardiovascular mortality					
#1	LD+cIMT	20	1.2	49.88	
#2	LD	19	2.64	24.27	3.74
#3	cIMT	19	2.74	23.06	3.93
#4	Null model	18	7.74	1.89	48.01
#5	LD/cIMT ratio	19	9.21	0.91	100.15

Likelihood and loss of information were represented in the calculated AIC for each model, which were ranked based on the difference in AIC (ΔAIC) between minimum calculated AIC and AIC of a model (AIC_i). The model with the lowest AIC was considered to have the highest support explaining mortality data. When using AIC, models with ΔAIC ≤2 are considered to have substantial support of having the highest explanatory value. Models within a 4 ≤ ΔAIC_i ≤7 range are considered to have some support, but considerably less than models with ΔAIC ≤2. Models with ΔAIC_i >10 have essentially no support. Akaike weights (AW) were calculated to provide the probability in percent of a model being the model with the highest support. Additionally, evidence ratios (ER) provide information on how more likely the model with minimum AIC is in relation to the respective model.[22] ΔAIC indicates AIC_i–AIC_{min}; AIC, Akaike information criterion; AW, Akaike weight; CiMT, carotid intima–media thickness; ER, evidence ratio; and LD, lumen diameter.

Table 4. Harrel's c Statistics Providing Information on the Predictive Power of the 4 Models

	Δcoefficient	95% CI
All-cause mortality, vs null model		
LD	0.0024	0.0005; 0.0042
cIMT	0.0006	−0.0005; 0.0016
LD+cIMT	0.0024	0.0005; 0.0043
LD/cIMT ratio	0.0002	−0.0002; 0.0005
All-cause mortality, vs LD		
cIMT	−0.0018	−0.0036; 0.0000
LD+cIMT	0.0000	−0.0006; 0.0005
LD/cIMT ratio	−0.0022	−0.0040; −0.0004
Cardiovascular mortality, vs null model		
LD	0.0001	−0.0013; 0.0035
cIMT	−0.0001	−0.0008; −0.0006
LD+cIMT	0.0011	−0.0013; 0.0035
LD/cIMT ratio	0.0006	−0.0013; 0.0025
Cardiovascular mortality, vs LD		
cIMT	−0.0011	−0.0036; 0.0013
LD+cIMT	0.0000	−0.0001; 0.0001
LD/cIMT ratio	−0.0005	−0.0027; 0.0017
Noncardiovascular mortality, vs null model		
LD	0.0028	0.0001; 0.0057
IMT	0.0017	−0.0012; 0.0047
LD+IMT	0.0034	0.0001; 0.0069
LD/IMT ratio	0.0001	−0.0008; 0.0010
Noncardiovascular mortality, vs LD		
IMT	−0.0011	−0.0045; 0.0022
LD+IMT	0.0005	−0.0016; 0.0027
LD/IMT ratio	−0.0027	−0.0058; 0.0004

cIMT indicates carotid intima–media thickness; and LD, lumen diameter.

95% CI, 1.14–1.48) and all-cause mortality remained significant. This was not the case when cIMT was the exposure variable (HR, 1.56; 95% CI, 0.92–2.64). The exclusion of individuals with stroke did not significantly change the results. However, while the relation between LD and LD+cIMT with all-cause mortality was not influenced because of the exclusion of individuals with type 2 diabetes mellitus (antidiabetic medication or HbA1c >6.5%) or prior myocardial infarction, cIMT lost significance (HR, 1.38; 95% CI, 0.51–3.79) (Figure 4).

DISCUSSION

This study compared associations and informative properties of common cIMT and LD with all-cause, cardiovascular and noncardiovascular mortality. Larger LDs were associated with greater mortality. Furthermore, the LD-based models consistently showed the best performance in information for each type of mortality as compared with the other models using AIC. Importantly, using LD significantly improved the model for all-cause mortality compared with cIMT and the null model (confounders only). Therefore, our results suggest that LD may be superior to cIMT.

Our results are in agreement with previous research. For example, a larger carotid diameter was associated with a higher risk for myocardial infarction and stroke.[3,25,26] These findings are supported by a large meta-analysis that included 4887 participants from 4 studies[18] and reported that carotid LD was associated with a greater risk for mortality. However, these 4 studies also displayed a large heterogeneity between studies (I^2 79%–86%, depending on model adjustment). Interestingly, when the authors adjusted for cIMT, the association between LD and all-cause mortality became nonsignificant. This was not the case in our analysis, and LD still provided significant information for the

Table 5. Results of the Cox Regression Models for Incident CVD and CHD

Parameter	Model	Incident CHD	Incident CVD
LD	1	1.20 (1.01; 1.52)*	1.19 (0.98; 1.42)
	2	1.23 (0.99; 1.51)	1.17 (0.97; 1.42)
	3	1.19 (0.96; 1.48)	1.10 (0.91; 1.34)
	4	1.19 (0.96; 1.48)	1.09 (0.89; 1.34)
	5	1.17 (0.93; 1.46)	1.06 (0.86; 1.30)
cIMT	1	1.01 (0.41; 2.51)	0.76 (0.33; 1.72)
	2	0.97 (0.39; 2.44)	0.73 (0.32; 1.67)
	3	0.85 (0.34; 2.16)	0.64 (0.27; 1.50)
	4	0.82 (0.32; 2.10)	0.59 (0.25; 1.40)
	5	0.69 (0.26; 1.83)	0.46 (0.18; 1.13)
LD+cIMT	1	1.27 (1.01; 1.60)*	1.24 (1.00; 1.53)*
	2	1.26 (1.00; 1.59)*	1.23 (0.99; 1.51)
	3	1.24 (0.97; 1.57)	1.16 (0.93; 1.44)
	4	1.24 (0.97; 1.58)	1.15 (0.92; 1.44)
	5	1.22 (0.96; 1.56)	1.12 (0.90; 1.40)
LD/cIMT	1	1.09 (0.96; 1.22)	1.09 (0.98; 1.21)
	2	1.08 (0.96; 1.22)	1.09 (0.99; 1.21)
	3	1.09 (0.97; 1.23)	1.09 (0.98; 1.21)
	4	1.09 (0.97; 1.23)	1.09 (0.98; 1.22)
	5	1.10 (0.98; 1.24)	1.11 (1.00; 1.23)*

Table 5—results of the Cox regression with regard to incident CVD and CHD. Shown are the hazard ratios per unit increase and 95% CI. CHD indicates coronary heart disease; CVD, cardiovascular disease; cIMT, carotid intima–media thickness; and LD, lumen diameter.

*Significant findings.

model. Furthermore, we did not only show a strong association between LD and mortality but also that LD provided more information with regard to incident CHD and CVD.

In our study, cIMT was not significantly associated with all-cause and CV mortality when individuals with previous myocardial infarction or type 2 diabetes mellitus were excluded. This may seem to contradict the general research consensus. However, a previous meta-analysis with data from 8 studies with 37 197 participants on the association of cIMT with incident cardiovascular events found a significant amount of heterogeneity (I^2 up to 61%) among the studies.[8] This heterogeneity was largely explained by varying study protocols, especially regarding sonography procedures and definitions of endpoints. Our results may be explained accordingly.

The distension of the coronary arteries during early stages of atherosclerosis has previously been described as the Glagov phenomenon.[10] A similar remodeling may also take place in the carotid arteries.[11,13] Previous studies explored the relation between carotid LD and established atherosclerotic risk factors. For example, a larger LD was positively associated with systolic blood pressure, body weight, prevalence of diabetes mellitus,[15] BMI,[27] and left ventricular mass.[28] All those risk factors are also positively associated with cIMT. However, a larger carotid LD may also be understood as a compensatory mechanism for increased cIMT.[3] These early changes in carotid LD may explain the greater information contained in LD compared with cIMT, as supported by our results. Our results may also be explained by the fact that the LD is much easier to measure compared with cIMT. The larger caliber of LD compared with cIMT may improve manual measurement accuracy and thus may be more applicable for an outpatient setting. However, we acknowledge that we did not compare the measurability of cIMT and LD.

The association between LD and cIMT with regard to cardiovascular risk factors revealed that low-density lipoprotein cholesterol was inversely associated with LD but positively with cIMT. This finding is in agreement with a recent publication that assessed the relation between LD and risk for a cardiovascular event.[18] Even though the authors did not specifically test for differences, the descriptive statistics show a concentration of 5.9 mmol/L (SD 1.0) in the lowest and 5.6 mmol/L (SD 1.0) in the highest LD tertile. One may speculate that this observation is because of lipid-lowering medication in subjects with a higher cardiovascular disease risk. Another possibility is that at the later atherosclerotic disease stages with a continuously increasing cIMT, a further compensatory enlargement of the LD is simply not possible. However, why this relationship is present for LD but not cIMT is currently not clear.

Our observation that LD and cIMT are associated with all-cause mortality when the models were additionally adjusted for atherosclerotic plaque was unexpected. However, both parameters are potential biomarkers for early subclinical alterations in the vasculature. Atherosclerotic plaque, on the other hand, is a clear sign of overt atherosclerotic disease. Hence, this finding should not detract from the main conclusion of our analysis, which was that models with LD had greater informative value for the all-cause and cardiovascular mortality in a general population-based setting. Nonetheless, atherosclerotic plaque was the most potent subclinical marker of mortality and CVD.

Limitations

We acknowledge several limitations in our analysis. First, SHIP comprised only Whites; further analyses of samples with other races are needed to evaluate the robustness of our findings. Second, our analyses were cross-sectional; consequently, we are not able to make any statements regarding causal relationships between the progression of LD and changes

Table 6. AIC Ranks for the 4 Tested Models Plus the Null Model (Set of Confounders Only) for the Different Adjustments

Adjusted for Age and Sex				Adjusted for Age, Sex, and Systolic Blood Pressure				Adjusted for Age, Sex, Systolic Blood Pressure, Current Smoking, Diabetes Mellitus, Cholesterol/HDL Ratio, BMI, and Triglycerides				Adjusted for Age, Sex, Systolic Blood Pressure, Current Smoking, Diabetes Mellitus, Cholesterol/HDL Ratio, BMI and Triglycerides, Lipid-Lowering Medication, Hypertensive Medication				Adjusted for Age, Sex, Systolic Blood Pressure, Current Smoking, Diabetes Mellitus, Cholesterol/HDL Ratio, BMI and Triglycerides, Lipid-Lowering Medication, Hypertensive Medication, Plaque			
Rank Model	ΔAIC	AW (%)	ER	Rank Model	ΔAIC	AW (%)	ER	Rank Model	ΔAIC	AW (%)	ER	Rank Model	ΔAIC	AW (%)	ER	Rank Model	ΔAIC	AW (%)	ER
Incident CVD																			
1. LD	0	27.93		1. LD/cIMT	0	28.64		1. LD/cIMT	0	33.73		1. LD/cIMT	0	35.67		1. LD/cIMT	0	39.28	
2. LD/cIMT	0.15	25.90	1.08	2. LD	0.32	24.44	1.17	2. Null model	0.74	23.28	1.45	2. Null model	0.99	21.80	1.64	2. cIMT	1.03	23.46	1.68
3. LD+cIMT	0.22	25.04	1.12	3. LD+cIMT	0.49	22.37	1.28	3. LD+cIMT	1.70	14.43	2.34	3. cIMT	1.61	15.98	2.23	3. LD+cIMT	1.84	15.65	2.51
4. Null model	1.30	14.56	1.92	4. Null model	1.09	16.60	1.73	4. LD	1.71	14.31	2.36	4. LD+cIMT	1.8	14.51	2.46	4. Null model	1.91	15.13	2.60
5. cIMT	2.89	6.57	4.25	5. cIMT	2.56	7.95	3.60	5. cIMT	1.72	14.25	2.37	5. LD	2.17	12.05	2.96	5. LD	3.6	6.48	6.06
Incident CHD																			
1. LD	0	46.65		1. LD	0	43.128		1. LD	0	31.68		1. LD	0	30.42		1. LD/cIMT	0	33.78	
2. LD+cIMT	1.42	22.93	2.04	2. LD+cIMT	1.38	21.62	1.99	2. LD/cIMT	0.57	23.87	1.33	2. LD/cIMT	0.39	25.01	1.22	2. LD	0.92	21.28	1.59
3. LD/cIMT	2.47	13.59	3.43	3. LD/cIMT	2.01	15.76	2.74	3. LD+cIMT	1.04	18.80	1.69	3. LD+cIMT	0.92	19.22	1.58	3. Null model	1.22	18.39	1.84
4. Null model	2.67	12.31	3.79	4. Null model	2.22	14.25	3.03	4. Null model	1.08	18.48	1.71	4. Null model	1.04	18.12	1.68	4. LD+cIMT	1.31	17.55	1.93
5. cIMT	4.66	4.53	10.3	5. cIMT	4.21	5.25	8.22	5. cIMT	2.97	7.17	4.42	5. cIMT	2.87	7.24	4.20	5. cIMT	2.64	9.00	3.75

Likelihood and loss of information were represented in the calculated AIC for each model, which were ranked based on the difference in AIC (ΔAIC) between minimum calculated AIC and AIC of a model (AIC_i). The model with the lowest AIC was considered to have the highest support explaining the incidence of cardiovascular disease or coronary heart disease. When using AIC, models with ΔAIC ≤2 are considered to have substantial support of having the highest explanatory value. Models within a $4 \leq \Delta AIC_i \leq 7$ range are considered to have some support, but considerably less than models with ΔAIC ≤2. Models with $\Delta AIC_i > 10$ have essentially no support. Akaike weights (AW) were calculated to provide the probability in percent of a model being the model with the highest support. Additionally, evidence ratios (ER) provide information on how more likely the model with minimum AIC is in relation to the respective model.[22] ΔAIC indicates $AIC_i - AIC_{min}$; AIC, Akaike information criterion; AW, Akaike weight; BMI, body mass index; CHD, coronary heart disease; cIMT, carotid intima–media thickness; CVD, cardiovascular disease; ER, evidence ratio; HDL, high-density lipoprotein cholesterol; and LD, lumen diameter.

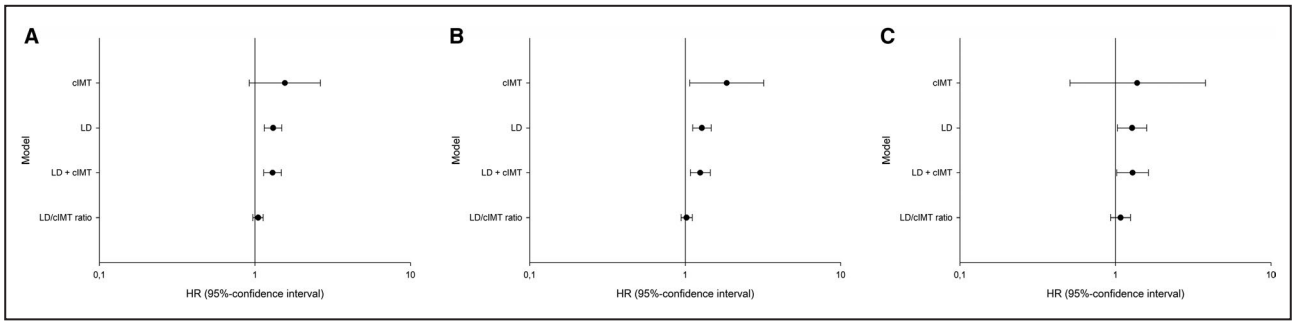

Figure 4. Forest plot with the 4 tested models for all-cause mortality after exclusion of subjects with chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2) (A), stroke (B), or type 2 diabetes mellitus (C).
HR for all-cause mortality are reported with 95% CIs for a 1-unit increase adjusting for all other variables in the model. cIMT indicates carotid intima–media thickness; HR, hazard ratios; LD, lumen diameter.

in mortality risk. Third, even though we have incorporated numerous confounders in our multivariable regression models, we cannot disregard the possibility of residual confounding. Fourth, we were unable to standardize the image recording to the cardiac cycle. Previous studies measured LD during systolic expansion of the artery. Thus, these measurements always had maximal dilation. This was not the case in our analysis and may have introduced an additional source of variation and potentially reduce statistical power. However, we used means of at least 6 images (3 from the right and 3 from the left side) with 3 measurements each to calculate our average lumen diameters. These values are very likely to be smaller than maximal dilation. We acknowledge that an automated or semi-automated method would have been better to measure luminal diameter. Yet, we observed a strong association between LD and mortality. Despite these limitations, our analyses also have some significant strengths, including the population-based sample, the large number of individuals of both sexes and a wide age range, the robust and well-standardized data set, and the adjustment for confounding. Furthermore, we believe that the incidence analysis with a 10-year follow-up demonstrated that LD significantly contributes to CVD risk.

CONCLUSIONS

To the best of our knowledge, this is the first study to compare the informative value of cIMT and LD with regard to all-cause, cardiovascular and noncardiovascular mortality associations. We report that LD provides more information than cIMT.

TRANSLATIONAL OUTLOOK

The identification of individuals with an increased risk for CVD is a hallmark in the preventative efforts of cardiologists worldwide. Our results suggest that the easily measurable LD could potentially be used to identify subjects with an increased risk not just for mortality but also for the development of CHD and CVD independent of other established clinical biomarkers. However, before risk stratification based on LD, future studies should reassess previously performed randomized clinical trials that used cIMT as an outcome and determine whether differences in LD because of pharmacological treatments can be found. Furthermore, longitudinal studies should investigate whether the LD increases with advancing age and whether this progression can be altered by pharmacological and nonpharmacological interventions.

ARTICLE INFORMATION

Received January 28, 2020; accepted July 6, 2020.

Affiliations

From the Department of Internal Medicine B, University Medicine Greifswald (F.F., S.G., S.B.F., M.D., M.B.), DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald (F.F., S.G., T.I., H.V., S.B.F., M.D., M.B.); Institute for Community Medicine (T.I., H.V.), and Department of Neurology, University Medicine Greifswald, Greifswald, Germany (U.S.).

Acknowledgments

Open access funding enabled and organized by Projekt DEAL.

Sources of Funding

This work was supported by grants from the German Federal Ministry of Education and Research (BMBF, grant number: 01ZZ96030 and 01ZZ0701).

Disclosures

None.

Supplementary Material

Table S1

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, et al.; American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.

2. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, et al. European Society of Cardiology: cardiovascular disease statistics 2017. *Eur Heart J*. 2018;39:508–579.
3. Bots ML, Grobbee DE, Hofman A, Witteman JC. Common carotid intima-media thickness and risk of acute myocardial infarction: the role of lumen diameter. *Stroke*. 2005;36:762–767.
4. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467.
5. Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaides AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. *Eur Heart J*. 1994;15:781–785.
6. Salonen R, Salonen JT. Carotid atherosclerosis in relation to systolic and diastolic blood pressure: Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Med*. 1991;23:23–27.
7. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J*. 2010;31:2041–2048.
8. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Volzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet*. 2012;379:2053–2062.
9. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging*. 2014;7:1025–1038.
10. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371–1375.
11. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. In vivo quantification of carotid arterial enlargement. The ARIC Investigators. *Stroke*. 1994;25:1354–1359.
12. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Risk factors and segment-specific carotid arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1996;27:69–75.
13. Polak JF, Kronmal RA, Tell GS, O'Leary DH, Savage PJ, Gardin JM, Rutan GH, Borhani NO. Compensatory increase in common carotid artery diameter. Relation to blood pressure and artery intima-media thickness in older adults. Cardiovascular Health Study. *Stroke*. 1996;27:2012–2015.
14. Mannami T, Baba S, Ogata J. Potential of carotid enlargement as a useful indicator affected by high blood pressure in a large general population of a Japanese city: the Suita study. *Stroke*. 2000;31:2958–2965.
15. Bonithon-Kopp C, Touboul PJ, Berr C, Magne C, Ducimetiere P. Factors of carotid arterial enlargement in a population aged 59 to 71 years: the EVA study. *Stroke*. 1996;27:654–660.
16. Kawamoto R, Tomita H, Oka Y, Ohtsuka N. Association between risk factors and carotid enlargement. *Intern Med*. 2006;45:503–509.
17. Leone N, Ducimetiere P, Gariepy J, Courbon D, Tzourio C, Dartigues JF, Ritchie K, Alperovitch A, Amouyel P, Safar ME, et al. Distension of the carotid artery and risk of coronary events: the three-city study. *Arterioscler Thromb Vasc Biol*. 2008;28:1392–1397.
18. Sedaghat S, van Sloten TT, Laurent S, London GM, Pannier B, Kavousi M, Mattace-Raso F, Franco OH, Boutouyrie P, Ikram MA, et al. Common carotid artery diameter and risk of cardiovascular events and mortality: pooled analyses of four cohort studies. *Hypertension*. 2018;72:85–92.
19. John U, Greiner B, Hensel E, Ludemann J, Piek M, Sauer S, Adam C, Born G, Alte D, Greiser E, et al. Study of Health in Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Soz Praventivmed*. 2001;46:186–194.
20. Volzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, Aumann N, Lau K, Piontek M, Born G, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol*. 2011;40:294–307.
21. Singh PN, Wang X. Simulation study of the effect of the early mortality exclusion on confounding of the exposure-mortality relation by preexisting disease. *Am J Epidemiol*. 2001;154:963–971.
22. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol*. 2008;8:70.
23. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33:261–304.
24. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
25. Eigenbrodt ML, Evans GW, Rose KM, Bursac Z, Tracy RE, Mehta JL, Couper DJ. Bilateral common carotid artery ultrasound for prediction of incident strokes using intima-media thickness and external diameter: an observational study. *Cardiovasc Ultrasound*. 2013;11:22.
26. Eigenbrodt ML, Sukhija R, Rose KM, Tracy RE, Couper DJ, Evans GW, Bursac Z, Mehta JL. Common carotid artery wall thickness and external diameter as predictors of prevalent and incident cardiac events in a large population study. *Cardiovasc Ultrasound*. 2007;5:11.
27. Chironi G, Gariepy J, Denarie N, Balice M, Megnien JL, Levenson J, Simon A. Influence of hypertension on early carotid artery remodeling. *Arterioscler Thromb Vasc Biol*. 2003;23:1460–1464.
28. Polak JF, Wong Q, Johnson WC, Bluemke DA, Harrington A, O'Leary DH, Yanez ND. Associations of cardiovascular risk factors, carotid intima-media thickness and left ventricular mass with inter-adventitial diameters of the common carotid artery: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2011;218:344–349.

SUPPLEMENTAL MATERIAL

Table S1. Extended baseline characteristics of the study population.

parameter	survivors	non-survivors	total
N	2,245 (81.61)	506 (18.39)	2,751
CV death n (%)		113 (22.33)	113 (4.1)
Non-CV deaths n (%)		179 (35.38)	179 (6.51)
female n (%)	1,265 (56.36)	175 (34.58)	1,440 (52.34)
age yr (SD)	49.78 (13.33)	69.29 (10.81)	53.37 (14.95)
hypertension n (%)	1,114 (49.62)	430 (84.98)	1,544 (56.13)
systolic BP mmHg (SD)	130.05 (18.65)	140.52 (21.22)	131.97 (19.57)
diastolic BP mmHg (SD)	81.76 (10.13)	79.66 (11.72)	81.37 (10.47)
current smoking n (%)	609 (27.13)	108 (21.34)	717 (26.06)
diabetes mellitus n (%)	173 (7.71)	147 (29.05)	320 (11.63)
BMI kg/m² (SD)	27.46 (4.7)	29.15 (4.9)	27.77 (4.77)
alcohol intake, last 30 days g/d (SD)	9.36 (13.33)	8.09 (13.35)	9.13 (14.01)
TG mmol/l (SD)	1.78 (1.77)	1.92 (1.27)	1.81 (1.69)
cholesterin mmol/l (SD)	5.57 (1.15)	5.38 (1.22)	5.54 (1.17)
HDLC mmol/l (SD)	1.21 (0.42)	1.07 (0.39)	1.19 (0.42)
LDLC mmol/l (SD)	3.54 (1.01)	3.45 (0.96)	3.52 (1.00)
Total cholesterol/HDLC ratio (SD)	0.63 (0.08)	0.64 (0.08)	0.63 (0.08)
creatinine µmol/l (SD)	68.14 (14.62)	81.06 (58.01)	70.47 (28.42)
eGFR ml/min (SD)	99.03 (16.04)	81.89 (19.8)	95.93 (18.03)
CRP mg/dl (SD)	1.85 (1.84)	2.64 (2.15)	1.96 (1.91)
blood glucose mmol/l (SD)	5.53 (1.16)	6.30 (2.1)	5.67 (1.41)
waist circumference cm (SD)	90.61 (13.55)	99.12 (12.87)	92.17 (13.82)
ultrasound parameters			
mean carotid LD, mm (SD)	6.17 (0.70)	6.85 (0.84)	6.29 (0.78)
mean max. IMT, mm (SD)	0.78 (0.15)	0.95 (0.21)	0.81 (0.17)
mean LD / IMT ratio, (SD)	8.09 (1.27)	7.49 (1.44)	7.98 (1.32)
income			
<500 EUR n (%)	42 (1.87)	13 (2.57)	55 (2.00)
500 - <900 EUR n (%)	209 (9.31)	60 (11.86)	269 (9.78)
900 - <1,300 EUR n (%)	345 (15.37)	122 (24.11)	467 (16.98)
1,300 - <1,800 EUR n (%)	519 (23.12)	164 (32.41)	683 (24.83)
1,800 - <2,300 EUR n (%)	457 (20.36)	92 (18.81)	549 (19.96)
2,300 - <2,800 EUR n (%)	287 (12.78)	34 (6.72)	321 (11.67)
2,800 - <3,300 EUR n (%)	179 (7.97)	15 (2.96)	194 (7.05)
≥3,300 EUR n (%)	207 (9.22)	6 (1.19)	213 (7.74)
level of education			
no degree n (%)	30 (1.34)	19 (3.75)	49 (1.78)
8/9 years of school n (%)	637 (28.37)	332 (65.61)	969 (35.22)

10 years of school n (%)	1,139 (50.73)	98 (19.37)	1,237 (44.97)
high school, college or university n (%)	439 (19.55)	57 (11.26)	496 (18.03)
plaque score			
0 n (%)	1,116 (49.71)	42 (8.30)	1,158 (42.09)
1 n (%)	477 (21.25)	86 (17.00)	563 (20.47)
2 n (%)	306 (13.63)	93 (18.38)	399 (14.50)
3 n (%)	271 (12.07)	180 (35.57)	451 (16.39)
4 n (%)	75 (3.34)	105 (20.75)	180 (6.54)
MetS n (%)	780 (36.76)	297 (61.75)	1,077 (41.38)
COPD n (%)	152 (6.77)	79 (15.61)	231 (8.40)
gout n (%)	124 (5.59)	61 (12.2)	185 (6.81)
atrial fibrillation n (%)	16 (0.72)	30 (6.12)	46 (1.69)
medications			
antidiabetic agents (ATC A10) n (%)	113 (5.03)	101 (19.96)	214 (7.78)
antithrombotic agents (ATC B01) n (%)	225 (10.02)	206 (40.71)	431 (15.67)
cardiac agents (ATC C01) n (%)	88 (3.92)	140 (27.67)	228 (8.29)
antihypertensive agents (ATC C02) n (%)	24 (1.07)	16 (3.16)	40 (1.45)
diuretics (ATC C03) n (%)	88 (3.92)	115 (22.73)	203 (7.38)
peripheral vasodilators (ATC C04) n (%)	11 (0.49)	21 (4.15)	32 (1.16)
beta-blocker (ATC C07) n (%)	454 (20.22)	216 (42.69)	670 (24.36)
calcium channel blockers (ATC C08) n (%)	123 (5.48)	114 (22.53)	237 (8.62)
cardio-spec. calcium channel blockers (ATC C08d) n (%)	16 (0.71)	23 (4.55)	39 (1.42)
RAAS modulators (ATC C09) n (%)	401 (17.86)	258 (50.99)	659 (23.95)
lipid lowering medication (ATC C10) n (%)	234 (10.42)	138 (27.27)	372 (13.52)
bronchodilators (ATC R03) n (%)	83 (3.7)	60 (11.86)	143 (5.20)

EUR; Euro; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation; TG: triacylglycerides; ATC: anatomical therapeutic chemical classification; COPD: chronic obstructive pulmonary disease; BMI: body mass index; RAAS: renin-angiotensin system; MetS: metabolic syndrome; eGFR: estimated glomerular filtration rate; HDLC: high density lipoprotein cholesterol; LDLC: low density lipoprotein cholesterol; CRP: C-reactive protein