Carotid Intima-Media Thickness and Incident ESRD: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background and objectives Carotid intima-media thickness has been reported to predict kidney function decline. However, whether carotid intima-media thickness is associated with a hard kidney end point, ESRD, has not been investigated.

Design, setting, participants, & measurements We studied 13,197 Atherosclerosis Risk in Communities participants at visit 1 (1987–1989) without history of cardiovascular disease, including coronary heart disease, stroke, and heart failure, at baseline and assessed whether carotid intima-media thickness measured by B-mode ultrasound is associated with ESRD risk using Cox proportional hazards models. Regarding carotid intima-media thickness parameters, we investigated the mean and maximum values of overall and segment-specific (common, bifurcation, and internal carotid arteries) measurements.

Results Mean age was 54.0 (SD=5.7) years old, and there were 3373 (25.6%) blacks and 7370 (55.8%) women. During a median follow-up of 22.7 years, 433 participants developed ESRD (1.4/1000 person-years). After adjusting for shared risk factors for atherosclerosis and kidney disease, including baseline kidney function, carotid intima-media thickness was significantly associated with ESRD risk (hazard ratio [HR] between quartiles 4 and 1, 1.46; 95% confidence interval [95% CI], 1.02 to 2.08 for overall mean intima-media thickness and HR between quartiles 4 and 1, 1.75; 95% CI, 1.24 to 2.48 for overall maximum intima-media thickness). The associations were largely consistent in demographic and clinical subgroups. When we explored segment–specific intima-media thicknesses, the associations with ESRD were most robust for bifurcation carotid (*e.g.*, adjusted HR between quartiles 4 and 1 of mean intima-media thickness, 1.49; 95% CI, 1.04 to 2.13 for bifurcation; adjusted HR between quartiles 4 and 1 of mean intima-media thickness, 1.36; 95% CI, 0.94 to 1.97 for common; and adjusted HR between quartiles 4 and 1 of mean intima-media thickness, 0.93; 95% CI, 0.67 to 1.29 for internal).

Conclusions Carotid intima-media thickness was independently associated with incident ESRD in the general population, suggesting the shared etiology of atherosclerosis and ESRD.

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Introduction

Atherosclerosis is characterized by arterial wall thickening caused by the deposition of plaque consisting of lipoprotein particles, macrophages, and smooth muscle cells (1,2). Representative risk factors for atherosclerosis include age, dyslipidemia, hypertension, cigarette smoking, and hyperglycemia (3–7). Atherosclerosis is a leading cause of coronary heart disease (CHD) and stroke. Although the incidence of atherosclerotic cardiovascular disease (CVD) has been decreasing over several decades, of note, it is still a leading cause of death in the United States (8,9).

Atherosclerosis can also affect kidney function through a few mechanisms. Atherosclerotic renal artery stenosis is a representative example and may lead to kidney dysfunction, mainly through hypertension caused by activated renin-angiotensin system (10). Indeed, as many as 14% of patients with ESRD have ESRD attributable to chronic ischemic nephropathy from renal artery stenosis (11). Moreover, some studies suggest the link between atherosclerosis of intrarenal vasculature and glomerulosclerosis (12). However, it is also possible that atherosclerosis and kidney disease merely share common pathogenic mechanisms or risk factors, such as diabetes and hypertension (13,14).

Elsayed *et al.* (15) have reported that kidney function declines faster among persons with atherosclerotic disease (CHD, stroke, and peripheral artery disease) than in those without it. However, treatment or clinical examinations in those with atherosclerotic disease (*e.g.*, iodinated contrast agent) may have confounded this association. In this connection, measures of subclinical atherosclerosis, such as carotid intima-media thickness (IMT), would be of value, and indeed, several studies have observed that increased carotid IMT predated kidney disease progression (16–19). However, most of them dealt with selected populations of older adults (16), whites (16,17), or

Asians (18), leaving uncertainty regarding their generalizability. Most importantly, none of the previous studies have evaluated ESRD, the most severe form of kidney disease with disproportionately high medical expenditure, as a kidney outcome.

Therefore, the primary objective of this study was to evaluate carotid IMT and its relationship to incident ESRD over 20 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study, a large community–based, predominantly biethnic cohort of middle-aged people.

Materials and Methods

Study Population

Details of the ARIC Study have been described elsewhere (20). Briefly, the ARIC Study is a prospective cohort of 15,792 individuals ages 45–64 years old from four United States communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD) at visit 1 (1987–1989). There were four follow-up examinations in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). Of 15,792 participants who attended visit 1, we excluded individuals who were neither white nor black (n=48), had missing data for carotid IMT (n=937), or had prevalent kidney failure (eGFR$<$15 ml/min per 1.73 m^2; n=21) or CVD, including CHD, stroke, or heart failure (n=1589), at baseline, leaving 13,197 individuals for this study. Of those 937 individuals without any carotid IMT data at baseline, 340 did not undergo the ultrasound examination, and 597 had unreadable scans. Possible reasons for having unreadable ultrasound scans include limitations in the ultrasound focal characteristics, ultrasound probe size, arterial depth and geometry, scanning and reading protocols, and sonographer and reader proficiency (21). Reflecting some of these possible reasons, participants without carotid IMT data had higher adiposity compared with those with carotid IMT measures, and thus, they were more likely to be diabetic and have higher BP (Supplemental Table 1). They were also more likely to be black. Prevalent CHD and stroke were defined as self-reported history before visit 1. Prevalent CHD also included evidence of a prior myocardial infarction by electrocardiogram (22). Prevalent heart failure was defined as self-reported treatment or Gothenburg stage 3 at visit 1 (23,24). All individuals provided written informed consent, and procedures were approved by the institutional review board at each study center.

Carotid IMT

Carotid IMT was measured from the blood-intimal to the medial-adventitial interface (25). The ultrasound measurements of the ARIC Study are on the basis of the technique validated by Pignoli *et al.* (25) using a scanning protocol common to the four field centers (26) and standardized central reading of scans (27). Carotid arteries were examined bilaterally at three sites: the level of the common carotid (1 cm proximal to the dilation of the carotid bulb), the carotid bifurcation (1 cm proximal to the flow divider), and the internal carotid artery (1 cm distal to the flow divider). In each 1-cm section, there were up to 11 measurements at 1-mm intervals (28). Carotid measures were adjusted for site–specific reader differences and downward measurement drifts over the baseline visit (28). We analyzed mean carotid IMT and maximum carotid IMT both overall and by carotid segments as exposures. Overall mean carotid IMT was defined as the mean of all carotid measurements along the far walls (farthest from the skin surface) at each of the six sites, whereas segment–specific mean carotid IMT was defined for each segment as the mean of far walls of both the left and right sides. For overall mean IMT, any missing sites were imputed from sex– and race–specific multivariate linear models of mean IMT as a function of age, body mass index (BMI), and arterial depth fitted by maximal likelihood methods as previously conducted in the ARIC Study (28,29). Overall maximum carotid IMT was defined as the maximum value from all carotid measured parameters of the far walls at the six sites, whereas segment–specific maximum carotid IMT was defined for each segment as the maximum far wall measurement from the left and right sides. For segment–specific maximum IMT, we rely on measured values without imputation, and thus, data are available in 13,106 individuals for common carotid IMT, 10,643 individuals for bifurcation IMT, and 8102 individuals for internal IMT.

Covariates

Information on demographics (age, sex, and race), lifestyle, and medical history was collected at visit 1 by trained interviewers using standardized questionnaires. Smoking status and alcohol intake were determined by self-report. BMI was calculated as weight in kilograms divided by the square of height in meters. Certified technicians used a random zero sphygmomanometer to measure BP three times with participants in the sitting position after 5 minutes of rest, and the average of the last two readings was recorded. Hypertension was defined as systolic BP $\geq$140 mmHg, diastolic BP $\geq$90 mmHg, or antihypertensive medication use. Diabetes mellitus was defined as a fasting glucose level $\geq$126 mg/dl, a nonfasting glucose level $\geq$200 mg/dl, self–reported physician diagnosis of diabetes, or use of glucose-lowering medications. Medication use was verified by inspection of medication bottles. Total cholesterol and HDL cholesterol were determined by enzymatic methods. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (30).

Outcome Assessment

Incident ESRD was defined as initiation of dialysis therapy, transplantation, or death caused by kidney disease (31). Patients with dialysis therapy and transplantation were identified by linkage to the US Renal Data System (USRDS), which captures information about all Americans with ESRD who receive RRT or are awaiting kidney transplantation (32). Death caused by kidney disease was defined as death with any of the following the 9th International Classification of Diseases (ICD-9) codes (as well as corresponding ICD-10 codes) in the primary code of the death certificate: kidney transplant (V42.0, 55.6, or 996.81), dialysis (V45.1, V56, 39.95, or 54.98), CKD (403, 404, 582, 583, 585, 585.3–585.5, 586, 587, 588, or 593.9), or diabetes with renal complications (250.4). Participants who were free of ESRD by December 31, 2011 were administratively censored.

Statistical Analyses

We first evaluated the Pearson correlation coefficients between carotid IMT and baseline eGFR. Carotid IMT parameters were primarily modeled using their quartiles (28,33). Therefore, baseline characteristics were summarized according to quartiles of overall mean carotid IMT, and differences were assessed by chi-squared test and ANOVA as appropriate. To visualize the potentially nonlinear association between overall mean and maximum carotid IMTs and ESRD, incidence rate of ESRD adjusted for age, sex, race, and center was evaluated using a Poisson regression model with linear spline terms of carotid IMT (three knots corresponding to cutoffs of its quartiles). We then quantified the association of each carotid IMT measure with incident ESRD using Cox proportional hazards models. We used two models with progressive adjustment. Model 1 adjusted for age, sex, race, center, and baseline eGFR. Model 2 also included systolic BP, antihypertensive medication, smoking, alcohol intake, BMI, total and HDL cholesterol, diabetes, and statin use. *P* value for linear trend was obtained by assigning the median value of each quartile of carotid IMT parameters to individuals in that quartile.

We conducted several sensitivity analyses. First, we examined the association in subgroups defined by age (<55 versus ≥55 years old), sex, race, diabetes, hypertension, obesity (BMI<30 versus ≥30 kg/m^2), and smoking. Because of low numbers of patients with ESRD in some of the subgroups, we estimated hazard ratios (HRs) comparing the highest quartile with the lower three quartiles for these subgroup analyses. The likelihood ratio test was used to test interactions. Second, we conducted competing risk analysis with death as a competing end point of ESRD. Third, we included incident CVD (CHD, stroke, and heart failure) events during follow-up as time-varying covariates. Incident CHD and stroke were defined as adjudicated patients after visit 1. Incident heart failure was defined as hospitalization for heart failure after visit 1 (23,24). All statistical analyses and graphical displays were performed using Stata, version 13.0 (StataCorp., College Station, TX).

Results

Mean age was 54.0 years old (SD=5.7), and there were 3373 (25.6%) blacks and 7370 (55.8%) women. Compared with those in the lowest quartile, participants with higher overall mean carotid IMT level were more likely to be older, black, smokers, and diabetic and have higher BMI and BP, abnormal lipid profile, and lower eGFR (Table 1). Overall mean and maximum IMT levels were correlated mildly with baseline eGFR (Pearson correlation coefficients =−0.14 and −0.09, respectively).

During a median follow-up of 22.7 years, there were 433 patients with ESRD (crude incidence rate =1.4/1000 person-years). After adjusting for age, sex, race, center, and baseline eGFR, overall, there was a graded association of overall mean IMT with incident ESRD, with risk gradient of two- to fourfold between the range in top and bottom quartiles (Figure 1A). Similar patterns were observed for overall maximum carotid IMT (Figure 1B). Additional adjustment for shared risk factors for atherosclerosis and kidney disease, such as BP, lipids, and diabetes, attenuated the association, but quartile 4 showed significantly higher risk of ESRD compared with quartile 1 (HR, 1.46; 95% confidence interval, 1.02 to 2.08 for overall mean IMT and HR, 1.75; 95% confidence interval, 1.24 to 2.48 for overall maximum IMT [model 2 in Table 2]). When restricting to patients with ESRD determined by USRDS linkage, we found similar results (Supplemental Table 2). The results were largely consistent in demographic and clinical subgroups that we tested, although we observed a significant interaction between races for overall maximum IMT (*P*=0.02), with a higher relative risk of ESRD according to high IMT in whites than in blacks (Figure 2).

Table 1. Baseline characteristics by quartiles of overall mean intima-media thickness

Variable	Overall	Quartile 1, *n*=3299	Quartile 2, *n*=3299	Quartile 3, *n*=3299	Quartile 4, *n*=3300	*P* Value[a]
Range, mm	0.37–2.28	0.37 to <0.62	0.62 to <0.70	0.70 to <0.81	≥0.81	
Age, yr	54.0±5.7	51.6±5.2	53.2±5.5	54.4±5.6	56.6±5.4	<0.001
Women, %	7370 (55.8)	2420 (73.4)	2044 (62.0)	1644 (49.8)	1262 (38.2)	<0.001
Black race, %	3373 (25.6)	744 (22.6)	896 (27.2)	865 (26.2)	868 (26.3)	<0.001
BMI, kg/m^2	27.3±5.0	26.1±4.9	27.2±4.9	27.9±5.1	27.9±4.9	<0.001
Systolic BP, mmHg	120.7±18.4	115.0±16.5	119.0±17.3	121.7±17.8	127.1±19.7	<0.001
Diastolic BP, mmHg	73.5±11.1	71.5±10.4	73.6±10.9	74.1±11.1	75.0±11.9	<0.001
Antihypertensive use, %	3273 (24.8)	618 (18.7)	761 (23.1)	846 (25.7)	1048 (31.8)	<0.001
Current smoker, %	3435 (26.1)	768 (23.3)	777 (23.6)	855 (25.9)	1035 (31.4)	<0.001
Current drinker, %	7547 (57.4)	1914 (58.2)	1892 (57.5)	1873 (57.0)	1868 (56.9)	0.67
Diabetes mellitus, %	1299 (9.9)	176 (5.4)	256 (7.8)	364 (11.1)	503 (15.3)	<0.001
Total cholesterol, mg/dl	214.3±41.5	206.5±40.8	212.6±40.6	216.5±40.3	221.8±42.7	<0.001
HDL cholesterol, mg/dl	54.0±17.7	58.9±18.5	55.1±18.0	52.1±17.0	49.8±15.8	<0.001
eGFR, ml/min per 1.73 m^2	102.9±14.9	105.0±14.3	104.3±14.2	102.5±14.9	99.9±15.5	<0.001

Quartiles of overall mean intima-media thickness expressed as millimeters. Values are presented as numbers (percentages); values for continuous variables are presented as means±SDs. BMI, body mass index.
[a]*P* values are on the basis of one-way ANOVA (for continuous variables) or chi-squared test (for categorical variables).

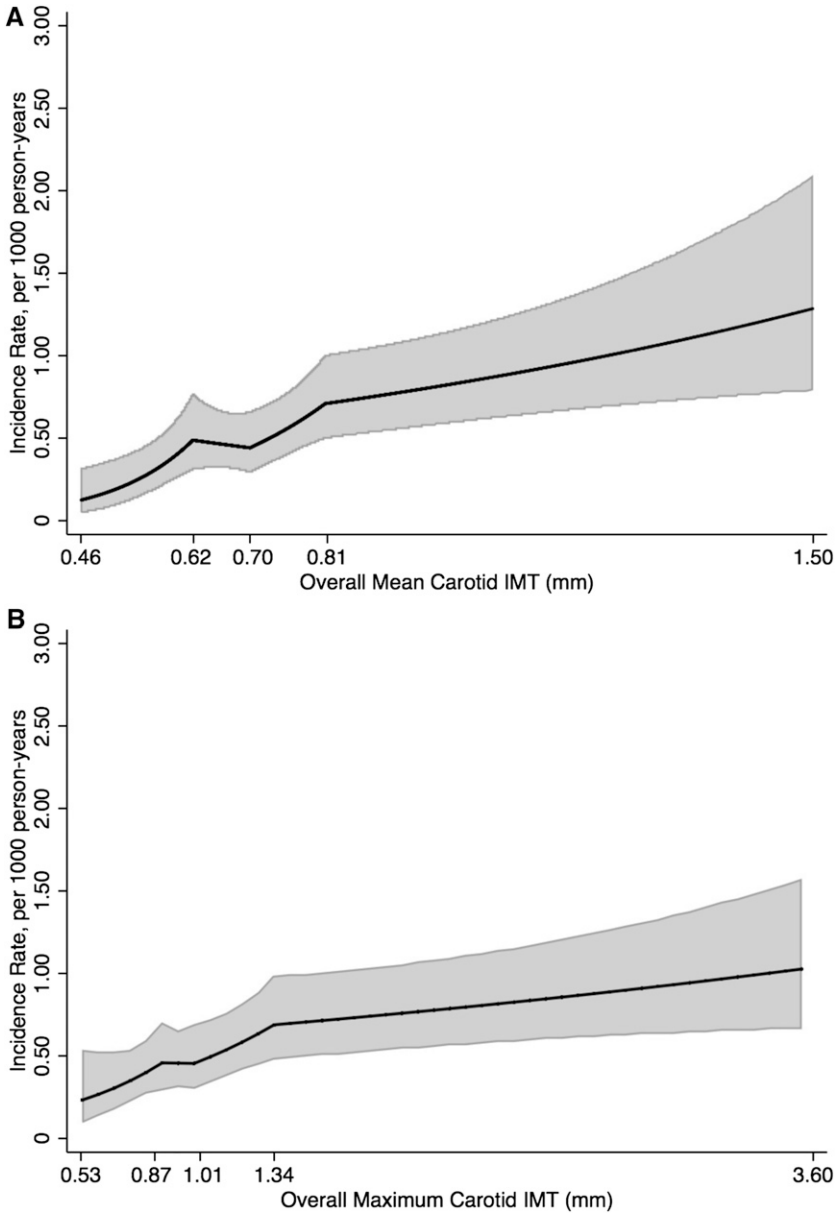

Figure 1. | Adjusted incidence rates of ESRD by overall mean carotid intima-media thickness (IMT) and overall maximum carotid IMT. Incidence rate per 1000 person-years was adjusted for age, sex, race, center, and eGFR and trimmed at 0.5% and 99.5%. Gray regions indicate the 95% confidence intervals of adjusted incidence rates. (A) indicates overall mean carotid IMT; (B) indicates overall maximum carotid IMT.

In competing risk analysis, an attenuated association was observed for overall mean IMT, but there was still a significant association for overall maximum IMT (Table 3). When incident CVD events were accounted for as time-varying covariates, the associations were attenuated and became nonsignificant for overall mean IMT, whereas they remained mostly significant for overall maximum IMT (Table 3). Among all CVD subtypes assessed, the adjustment for heart failure attenuated the associations the most.

When we explored segment-specific IMTs, the associations with ESRD were most robust for bifurcation IMT, regardless of whether its mean or maximum value was used (Table 4). The mean and maximum common carotid IMTs showed a more evident dose-response relationship than bifurcation IMT in model 1, but the associations were considerably attenuated after accounting for potential confounders, particularly when its mean value was analyzed. The associations of internal IMT and ESRD risk were overall weak and no longer significant in model 2.

Discussion

We found that greater overall carotid IMT levels were associated with incident ESRD in the general population independent of shared risk factors for atherosclerosis and kidney disease. The elevated risk of ESRD was particularly evident in the top quartile of carotid IMT. Although mean and maximum carotid IMTs showed similar results, overall, the associations tended to be stronger for maximum

Table 2. Hazard ratios (95% confidence intervals) of incident ESRD by quartiles of overall intima-media thickness

Model	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value for Trend
Overall mean					
Range, mm	0.37 to <0.62	0.62 to <0.70	0.70 to <0.81	≥0.81	
Model 1[a]	Reference	1.26 (0.87 to 1.83)	1.56 (1.10 to 2.23)	2.52 (1.79 to 3.55)	<0.001
Model 2[b]	Reference	1.13 (0.77 to 1.64)	1.05 (0.73 to 1.52)	1.46 (1.02 to 2.08)	0.01
Overall maximum					
Range, mm	0.27 to <0.87	0.87 to <1.01	1.01 to <1.34	≥1.34	
Model 1[a]	Reference	1.28 (0.87 to 1.89)	1.48 (1.04 to 2.09)	2.42 (1.73 to 3.40)	<0.001
Model 2[b]	Reference	1.16 (0.78 to 1.72)	1.19 (0.83 to 1.69)	1.75 (1.24 to 2.48)	<0.001

[a]Model 1: Adjusted for age, sex, race, center, and eGFR.
[b]Model 2: Adjusted for variables in model 1 plus systolic BP, antihypertensive medication, smoking status, alcohol intake, body mass index, total and HDL cholesterol levels, diabetes, and statin use.

IMT than for mean IMT in our study. These associations were attenuated after controlling for incident CVD events during follow-up, particularly when we accounted for incident heart failure. Although the association between maximum carotid IMT and ESRD risk was greater in whites than in blacks, overall, qualitatively consistent results were seen in several demographic and clinical subgroups. Regarding specific carotid segments, we found that IMT at bifurcation seemed to be most robustly associated with ESRD risk.

Our results are largely consistent with previous studies reporting the associations of increased carotid IMT levels with incident reduced kidney function and kidney function decline (16–18). We extended the results from previous studies by confirming the association with ESRD, a hard kidney outcome with great clinical and social importance. Also, it was important to confirm this association in blacks. Moreover, we comprehensively assessed both mean and maximum values of carotid IMT and systematically investigated segment-specific IMT. We also tried to apply sophisticated statistical approaches, such as spline modeling, competing risk, and time–varying covariate analysis for incident CVD events.

There are several potential mechanisms linking atherosclerosis to elevated ESRD risk. Atherosclerosis and ESRD are known to share risk factors, such as hypertension and

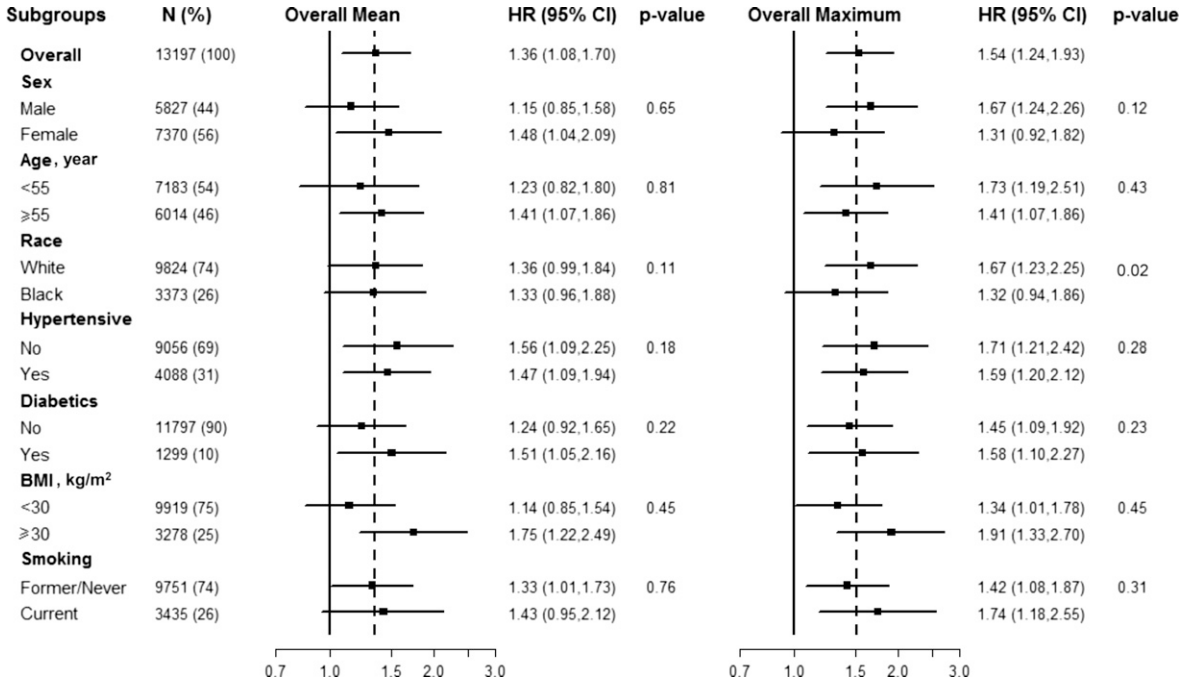

Figure 2. | Adjusted hazard ratio (HR) of ESRD comparing the highest quartile with the lower three quartiles in subgroups. Adjustment was on the basis of model 2 (age, sex, race, center, systolic BP, antihypertensive medication, smoking status, alcohol intake, body mass index (BMI), total and HDL cholesterol levels, diabetes, statin use, and eGFR). 95% CI, 95% confidence interval.

Table 3. Hazard ratios (95% confidence intervals) of incident ESRD by top versus bottom quartiles of intima-media thickness on the basis of competing risk model and cardiovascular disease as time-varying covariates

IMT Parameter	Competing Risk[a]	CHD	Stroke	Heart Failure
Overall mean	1.33 (0.91 to 1.95)	1.32 (0.92 to 1.88)	1.40 (0.98 to 2.00)	1.26 (0.87 to 1.81)
Overall maximum	1.66 (1.15 to 2.39)	1.61 (1.13 to 2.29)	1.71 (1.20 to 2.42)	1.40 (0.98 to 2.00)

Adjusted for age, sex, race, center, systolic BP, antihypertensive medication, smoking status, alcohol intake, body mass index, total and HDL cholesterol levels, diabetes, statin use, and eGFR. For incident cardiovascular disease, models were further adjusted for time-varying CHD, stroke, and heart failure. IMT, intima-media thickness; CHD, coronary heart disease.
[a]The competing risk model is competing risk for death.

diabetes (13,14). However, the associations of carotid IMT with ESRD remained significant after the adjustment for those factors, suggesting the independent contribution of subclinical atherosclerosis to the development of ESRD. This independent association may be because of the property of IMT reflecting the past profile of those risk factors over time. In this context, renal artery stenosis is a representative atherosclerotic disease linked to kidney dysfunction and may damage the kidney through hypertension because of the activated renin-angiotensin system (10,11). Moreover, Kasiske (12) found a significant and independent relationship between intrarenal arterial wall thickness and a number of sclerotic glomeruli on the basis of autopsy data.

Despite these potential mechanisms linking atherosclerosis to kidney disease progression, randomized controlled trials have yielded inconclusive results regarding whether statin can prevent kidney disease progression (34–36). However, we need to keep in mind that most previous statin trials were designed to assess the prevention of cardiovascular outcomes and underpowered to evaluate renoprotection (34–36). Given that the significant association with ESRD risk was observed primarily in the top quartile of carotid IMT, it may be that statin therapy is particularly effective in the prevention of kidney disease progression among people with higher burdens of subclinical atherosclerosis.

Table 4. Hazard ratios (95% confidence intervals) of incident ESRD by quartiles of intima-media thickness for different carotid segments

Model	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value for Trend
Mean common					
Range, mm	0.30 to <0.57	0.57 to <0.64	0.64 to <0.73	≥0.73	
Model 1[a]	Reference	1.48 (1.01 to 2.17)	1.93 (1.34 to 2.79)	2.39 (1.67 to 3.43)	<0.001
Model 2[b]	Reference	1.22 (0.83 to 1.80)	1.38 (0.96 to 2.01)	1.36 (0.94 to 1.97)	0.14
Mean bifurcation					
Range, mm	0.33 to <0.68	0.68 to <0.79	0.79 to <0.92	≥0.92	
Model 1[a]	Reference	1.18 (0.81 to 1.72)	1.64 (1.15 to 2.34)	2.41 (1.71 to 3.40)	<0.001
Model 2[b]	Reference	1.03 (0.70 to 1.51)	1.25 (0.87 to 1.80)	1.49 (1.04 to 2.13)	<0.01
Mean internal					
Range, mm	0.25 to <0.57	0.57 to <0.66	0.66 to <0.77	≥0.77	
Model 1[a]	Reference	0.94 (0.67 to 1.32)	1.32 (0.96 to 1.80)	1.61 (1.18 to 2.19)	<0.001
Model 2[b]	Reference	0.76 (0.54 to 1.07)	0.94 (0.68 to 1.29)	0.93 (0.67 to 1.29)	0.85
Maximum common					
Range, mm	0.27 to <0.74	0.74 to <0.87	0.87 to <1.01	≥1.01	
Model 1[a]	Reference	1.11 (0.71 to 1.74)	1.45 (0.94 to 2.25)	2.05 (1.35 to 3.11)	<0.001
Model 2[b]	Reference	1.11 (0.70 to 1.75)	1.21 (0.78 to 1.90)	1.43 (0.93 to 2.20)	0.03
Maximum bifurcation					
Range, mm	0.20 to <0.80	0.80 to <1.01	1.01 to <1.34	≥1.34	
Model 1[a]	Reference	0.95 (0.64 to 1.40)	1.10 (0.76 to 1.60)	1.86 (1.31 to 2.63)	<0.001
Model 2[b]	Reference	0.95 (0.63 to 1.41)	1.03 (0.70 to 1.51)	1.45 (1.01 to 2.08)	<0.01
Maximum internal					
Range, mm	0.20 to <0.60	0.60 to <0.74	0.74 to <1.01	≥1.01	
Model 1[a]	Reference	0.87 (0.54 to 1.39)	0.92 (0.60 to 1.41)	1.32 (0.86 to 2.02)	0.05
Model 2[b]	Reference	0.89 (0.55 to 1.44)	0.91 (0.59 to 1.40)	1.11 (0.72 to 1.72)	0.35

[a]Model 1: Adjusted for age, sex, race, center, and eGFR.
[b]Model 2: Adjusted for variables in model 1 plus systolic BP, antihypertensive medication, smoking status, alcohol intake, body mass index, total and HDL cholesterol levels, diabetes, and statin use.

Although similar associations were observed in the demographically adjusted model, overall maximum IMT showed a stronger association with ESRD than overall mean when further adjusting for shared risk factors. Overall maximum IMT also displayed a more robust association with ESRD when accounting for incident CVD events as time-varying covariates. None of the previous studies investigating the association of carotid IMT with kidney dysfunction have compared mean and maximum IMTs in this regard (16–18). However, our findings seem consistent with the observations that maximum carotid IMT shows stronger associations with CVD events compared with mean IMT in some studies (37–39). Although this finding warrants confirmation in other studies, it is possible that atherosclerosis does not occur equally in every vascular bed, and maximum IMT may represent the pathologic atherosclerotic process better than mean IMT. It is also possible that maximum IMT reflects the presence of plaque more than mean IMT and that plaque may be important in predicting ESRD risk.

Among all segments assessed, the associations of IMT levels with ESRD were most robust for bifurcation carotid and least robust for internal carotid. This may be partially because of the precision of measurement in each site. Indeed, in the ARIC Study, intraclass correlation coefficients between repeated assessments by different sonographers and different readers were 0.77 for bifurcation, 0.73 for common, and 0.70 for internal far wall IMT (40). Also, it is possible that bifurcation reflects atherosclerotic burden better than other segments. Indeed, the physiologic predisposition of atherosclerosis in carotid bifurcation is well known, possibly because of geometry, velocity profile, and shear stress (41,42). Low shear stress, which is associated with endothelial damage, preferentially affects the outer edges of vessel bifurcations (41). Findings from flow analysis and carotid endarterectomy showed that the greatest plaque thickness occurs in the outer wall of carotid bifurcation (42). Autopsy studies have also shown that the most frequent site for atherosclerosis is carotid bifurcation (43,44).

Among CVD subtypes that we accounted for as a time-varying covariate, incident heart failure attenuated the associations of carotid IMT with ESRD the most. This may suggest that heart failure is an important mediator between subclinical atherosclerosis and ESRD risk. Indeed, ischemic heart disease is a major cause of heart failure, and patients with heart failure are known to be at high ESRD risk because of decreased kidney perfusion from low cardiac output and diuretic therapy and excessive activation of the renin-angiotensin-aldosterone system (45–47). Nevertheless, this finding may highlight the importance of following up kidney function among those with atherosclerosis, particularly when they develop heart failure in the clinical course.

This study has several limitations. First, because of data unavailability at visit 1 in the ARIC Study, we were not able to adjust for albumin-to-creatinine ratio, a potent risk factor for ESRD other than eGFR (48). Second, there were a limited number of ESRD events in participants of certain quartiles of carotid IMT, and thus, we may not have enough power in certain strata in subgroup analysis. Third, as an observational study, this study may not be exempt from residual confounding (for example, related to inflammation and oxidative stress) (49,50). Fourth, as mentioned above, approximately 5% of the ARIC Study participants (937 of 15,792) did not have carotid IMT data usable for this study and had unique characteristics compared with the final study population (*e.g.*, higher likelihood of obesity and blacks). This may somewhat question generalizability of our findings, but it is important that we confirmed consistent results, regardless of these clinical and demographic factors.

In summary, greater carotid IMT levels were independently associated with incident ESRD in a biethnic middle–aged general population. The associations were largely consistent in several demographic and clinical subgroups. These findings suggest the shared etiology of atherosclerosis and ESRD.

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Disclosures

None.

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