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Maximum Carotid Intima-Media Thickness in Association with Renal Outcomes

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Aim: We aimed to examine the association between the maximum intima-media thickness of the carotid artery (Max IMT) and renal prognosis, considering their potential interaction with age.

Methods: Survival analyses were performed in 112 patients with chronic kidney disease (CKD), to assess renal prognosis, with the endpoint defined as a ≥ 30% decline in estimated glomerular filtration rate (eGFR) or end-stage renal disease.

Results: During a median follow-up of 12.5 years, 44 participants reached the study endpoint. The major determinant of Max IMT was the maximum IMT of the internal carotid artery (Max ICA-IMT), which was the distribution ratio of 50.0% of Max IMT. Kaplan–Meier analyses showed that Max IMT ≥ 1.5 mm was significantly associated with renal prognosis when age and eGFR were matched. On multivariate Cox regression analysis, Max IMT was significantly associated with the renal outcomes and had a significant interaction with the age categories (≥ 65 years or <65 years) (P=0.0153 for interaction). A 1-mm increase in Max IMT was significantly associated with disease progression in the sub-cohort <65 years age-category, but not in the ≥ 65 years age-category; similarly the hazard ratio (HR) in the <65 years age-category was higher than in the ≥ 65 years age-category (HR: 2.52 vs. 0.95). Comparable results were obtained for Max ICA-IMT, Max bulb-IMT, but not for Max common carotid artery-IMT.

Conclusions: A higher Max IMT was a significant renal prognosis factor in patients with CKD aged <65 years. Our results may provide new insights into treating CKD.

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Key words: Maximum carotid intima-media thickness, Chronic kidney disease, Prognosis, Interactions, Elderly

Introduction

Carotid intima-media thickness (IMT), provided by innocuous and repeatable B-mode ultrasound, has associations with cardiovascular diseases (CVDs)[1-4], and measuring carotid IMT is thought to be useful to refine risk assessment for patients at intermediate CVD risk[5, 6]. In the Framingham Offspring Study[1], a maximum IMT of the internal carotid artery (Max ICA-IMT) >1.5 mm significantly added predictive value to the Framingham risk score. In a Japanese study of 1,358 men aged 60 to 74 years[2], those with Max IMT ≥ 1.5 mm had a 3-fold higher risk of stroke than those with Max IMT <1.5 mm. Furthermore, among patients with coronary artery disease with a maximum IMT of the common carotid artery (Max CCA-IMT) ≥ 1.1 mm, progression of the Max CCA-IMT was associated with future coronary events[4]. Recently, Polak *et al.*[6] made the assertion that ICA-IMT and CCA-IMT represent different phenotypes,

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because of the different characteristics of their association with risk factors[7, 8].

On the other hand, in the field of nephrology, atherosclerotic vascular damage is now considered a common pathway for cardiac failure and renal dysfunction[9-11]. It has been reported that an increased carotid IMT is associated with albuminuria progression[12] and incident chronic kidney disease (CKD)[13]. However, until recently, longitudinal studies evaluating carotid IMT as a predictor of kidney function decline in patients with CKD were lacking, and whether the carotid IMT is useful for predicting kidney disease progression remained unclarified[14]. More recently, a few studies reported that an increased carotid IMT is associated with CKD progression in diabetic patients[15, 16] and end-stage renal disease (ESRD) in the general population[17]. However, these previous studies included patients without CKD; no study has exclusively focused on patients with CKD. Furthermore, in these former studies, renal function was lower in the group with increased carotid IMT than in other groups. Considering the fact that age[16, 17] and decreased renal function[16-18], which are also risk factors of CKD progression, were associated with increased carotid IMT, a study that eliminates the effects of age and renal function is desired.

This study aimed firstly to examine the association between Max IMT and renal outcomes in patients with CKD, with consideration of a potential interaction with age, and secondly, to confirm the association between renal prognosis and Max IMT ≥ 1.5 mm using a cohort matched for age, sex, glycemic control status, and estimated glomerular filtration rate (eGFR).

Patients and Methods

Study Population

We screened 2012 outpatients with CKD who visited the Kidney Center at Tokyo Women's Medical University Hospital in Japan between August 2006 and August 2007. Among these, 113 patients underwent B-mode ultrasound. After excluding one patient with nephrotic syndrome, 112 patients were ultimately enrolled and prospectively evaluated in the present study **(Supplementary Fig. 1)**. CKD was diagnosed according to previously described criteria[19]. The subjects' human rights and methods for protecting their personal information were considered in detail. All the relevant and responsible staff adhered to the principles of the Helsinki Declaration (amended October 2013) and the Ethical Guidelines for Clinical Studies (revised February 28, 2017; referred to hereafter as the Clinical Studies Ethical Guidelines) in the execution of this study. This cohort study was approved by the Medical Ethics Committee of Tokyo Women's Medical University (#4599). All participants gave their written informed consent at the time of entry.

Covariate Assessments

Anthropometric and physical examinations for baseline characteristics, including blood pressure components, body height, body weight, body mass index, and Max IMTs, were conducted during a regular outpatient clinic visit. Blood pressure was measured in triplicate using a mercury sphygmomanometer, and the average value was used in analysis. Max IMTs were measured using B-mode ultrasound. All biochemical analyses were performed on samples obtained after overnight fasting. Serum creatinine levels were enzymatically measured. The eGFR was calculated using a previously described formula for Japanese patients[20]. Concomitant drug use (antihypertensive drugs, diuretics, and medications for hyperuricemia, dyslipidemia, and diabetes mellitus) and comorbidities at the time of entry were assessed[21]. Definitions of comorbidities and primary causes of CKD are presented in the Supplementary Methods. Patients were followed up until December 31, 2019.

Carotid Ultrasonography

All carotid ultrasound examinations were performed by experienced and centrally-trained vascular sonographer specialists blinded to patient data using ultrasonographic B-mode imaging of the carotid artery via a high-resolution real-time ultrasonograph with a 12-MHz in-line Sectascanner (SSA-390A; Aloka, Tokyo, Japan). Carotid ultrasonic examinations were based on previous reports[5, 22]. Briefly, for this examination, after the patients rested in the supine position for at least 10 min, their neck was placed in a slightly hyperextended position and optimal bilateral visualization of the carotid arteries was performed. The scan was performed with image acquisition at the near and far walls of the right and left CCAs, carotid bulbs, and ICAs. Max IMT was defined as the maximum measurable IMT in the entire scanned CCAs, carotid bulbs, and ICAs. We also evaluated the component of Max IMT: Max CCA-IMT, Max bulb-IMT, and Max ICA-IMT. All patients received carotid ultrasonography at the baseline visit or before and after the baseline visit.

Study Endpoint

The endpoint of the study was kidney disease progression, which was defined as a ≥ 30% decline in eGFR from baseline (≥ 30% eGFR decline) or the development of ESRD requiring dialysis.

Statistical Analysis

Continuous variables are expressed as means and standard deviations (SDs) or as medians (quartile 1, quartile 3). Categorical variables are expressed as percentages unless otherwise stated. Group differences were evaluated using the unpaired *t*-test, Mann-Whitney *U* test, Chi-square test, or Fisher's exact test, as appropriate. Univariate and multivariate linear regression analyses were performed to determine the factors associated with the baseline Max IMT level. Odds ratios were estimated by using logistic regression analysis. Univariate and multivariate Cox proportional hazards analyses were performed to determine the variables associated with renal outcomes. Variables with $P<0.1$ on the univariate analysis, as well as age, sex, eGFR, and interaction terms (all variables * age ≥ 65 years), were included in the primary multivariate analyses. Subgroup analyses were performed by dividing patients into two pre-specified subgroups, namely a high Max IMT group (Max IMT ≥ 1.5 mm) and a low Max IMT group (Max IMT <1.5 mm). Survival curves were plotted using the Kaplan–Meier method and evaluated using the log-rank test. To reduce confounding biases, in patients with stage 3 CKD, we fitted propensity score-matched models that included potentially modifying variables, namely, age, sex, hemoglobin A1c, and eGFR. The caliper-matching method was used, with a maximum tolerance level of 0.2. *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using JMP Pro software, Windows v15.0.0 (SAS Institute, North Carolina, USA).

Results

Patient Characteristics

Table 1 presents the baseline characteristics according to the Max IMT category. The 112 participants comprised 55 patients with Max IMT <1.5 mm and 57 patients with Max IMT ≥ 1.5 mm, with a mean age at baseline of 63.0 ± 10.3 years (range: 24–83 years). Distribution ratio of Max-IMT were CCA/ bulb /ICA = 16.1%/ 33.9%/ 50.0%, and the major determinant of Max-IMT was the Max ICA-IMT. The median follow-up duration was 12.5 years (interquartile range: 4.1–12.9 years), and 44 patients showed disease progression (i.e., a ≥ 30% eGFR decline or the development of ESRD) during the follow-up period. Comparative analyses revealed that the patients with Max IMT ≥ 1.5 mm had an older age, a higher percentage of men, higher levels of triglycerides, and higher Max IMTs, and lower levels of serum albumin and high-density lipoprotein (HDL) cholesterol than the patients with Max IMT <1.5 mm. Regarding concomitant drugs and comorbidity rates, anti-dyslipidemic agent use, hypertriglyceridemia, and low HDL cholesterol were more frequent in patients with Max IMT ≥ 1.5 mm than in patients with Max IMT <1.5 mm **(Table 1)**. **Supplementary Table 1** provides the results of the propensity score-matched models based on age, sex, hemoglobin A1c, and eGFR. There were no significant differences between the propensity score-matched groups in any of the parameters except anti-hyperuricemic agent use (Max IMT ≥ 1.5 mm vs. Max IMT <1.5 mm: 26.3% vs. 63.2%, $P=0.0489$), and Max IMTs **(Supplementary Table 1)**. **Supplementary Table 2** provides the baseline characteristics according to age category (age ≥ 65 years or <65 years).

3.2. Correlations between the Maximum Carotid Intima-Media Thickness and other Parameters

Since Max IMT values may be affected by confounders, baseline Max IMT values were tested for any correlations with clinical and laboratory parameters at baseline **(Supplementary Table 3)**. On univariate analysis, Max IMT was significantly correlated with age ($\beta=0.35$; $P=0.0002$), male sex ($\beta=0.36$; $P=0.0001$), HDL cholesterol ($\beta=-0.19$; $P=0.0483$), and hs-CRP ($\beta=0.36$; $P=0.0001$). On multivariate linear regression analysis, Max IMT was correlated with age ($\beta=0.32$; $P=0.0003$), male sex ($\beta=0.30$; $P=0.0013$), and hs-CRP ($\beta=0.23$; $P=0.0075$).

3.3. Maximum Carotid Intima-Media Thickness as a Progression-Related Factor in Patients with Chronic Kidney Disease

The results of the univariate and multivariate Cox regression analyses for the entire cohort are provided in **Table 2**. On univariate Cox regression analysis, age, eGFR, urine albumin-to-creatinine ratio, Max bulb-IMT, Max ICA-IMT, and Max IMT were significantly associated with disease progression in the entire cohort. In contrast, Max CCA-IMT was not associated with renal prognosis in the entire cohort. After adjusting for age, sex, eGFR, UACR, and interaction terms (all variables * age ≥ 65 years), the multivariate Cox regression analyses revealed Max bulb-IMT, Max ICA-IMT, and Max IMT as independent risk factors for CKD progression in the entire cohort. In terms of CKD progression, significant interactions of age category (age ≥ 65 years) with Max ICA-IMT ($P=0.0490$ for the interaction) and Max IMT ($P=0.0153$ for the interaction) were revealed **(Table 2)**. Regarding Max IMT, similar results were obtained from the multivariate Cox regression analyses, which included more variables such as hypertriglyceridemia, low HDL cholesterol, and anti-dyslipidemic agents, as well as age, sex,

Table 1. Patient characteristics according to the levels of the maximum intima–media thickness of the carotid artery (Entire cohort: $n=112$)

Variables	Entire Cohort	Max IMT < 1.5 mm	Max IMT ≥ 1.5 mm	*P*-Value	*SD*
	$n=112$	$n=55$	$n=57$		
Clinical Findings					
Age (years)	63.0 ± 10.3 [112]	58.7 ± 9.9	67.1 ± 9.1	< 0.0001	0.883
Gender (Men; %)	66 (58.9) [112]	24 (43.6)	42 (73.7)	0.0012	0.642
SBP (mmHg)	126.2 ± 6.7 [112]	126.2 ± 6.7	126.2 ± 6.7	0.9805	0.000
DBP (mmHg)	77.4 ± 5.0 [112]	77.6 ± 4.8	77.2 ± 5.3	0.6953	0.079
MBP (mmHg)	93.6 ± 5.4 [112]	93.8 ± 5.3	93.5 ± 5.4	0.7977	0.056
BMI (kg/m^2)	24.5 ± 3.4 [112]	24.3 ± 3.3	24.6 ± 3.6	0.6845	0.087
Max CCA-IMT (mm)	0.9 (0.8–1.3) [112]	0.8 (0.7–0.9)	1.2 (0.8–1.7)	< 0.0001	0.966
Max bulb-IMT (mm)	1.2 (0.9–1.7) [88]	0.9 (0.8–1.2)	1.7 (1.3–2.3)	< 0.0001	1.490
Max ICA-IMT (mm)	1.6 (1.2–2.4) [82]	1.1 (0.9–1.2)	2.0 (1.6–3.3)	< 0.0001	1.665
Max IMT (mm)	1.5 (1.2–2.2) [112]	1.2 (0.9–1.2)	2.1 (1.8–3.2)	< 0.0001	2.069
Distribution ratio of Max-IMT: CCA/ bulb /ICA	18 (16.1)/ 38 (33.9)/ 56 (50.0) [112]	11 (20.0)/ 24 (43.6)/ 20 (36.4)	7 (12.3)/ 14 (24.6)/ 36 (63.2)	0.0178	NA
Laboratory Findings					
Serum Albumin (g/dL)	4.22 ± 0.28 [112]	4.29 ± 0.27	4.16 ± 0.28	0.0216	0.473
Hemoglobin (g/dL)	13.5 ± 1.7 [112]	13.7 ± 1.7	13.3 ± 1.8	0.2575	0.228
Serum Creatinine (mg/dL)	1.18 ± 0.82 [112]	1.15 ± 0.92	1.20 ± 0.72	0.7359	0.061
eGFR ($mL/min/1.73\ m^2$)	56.0 ± 20.6 [112]	59.0 ± 22.1	53.1 ± 18.9	0.1327	0.287
CKD stage 1/ 2/ 3a/3b/4/5 (%)	5 (4.5)/ 40 (35.7)/ 37 (33.0)/ 16 (14.3)/ 10 (8.9)/ 4 (3.6) [112]	2 (3.6)/ 25 (45.5)/ 16 (29.1)/ 4 (7.3)/ 5 (9.1)/ 3 (5.5)	3 (5.3)/ 15 (26.3)/ 21 (36.8)/ 12 (21.1)/ 5 (8.8)/ 1 (1.8)	0.1383	NA
Uric Acid (mg/dL)	5.82 ± 1.42 [112]	5.58 ± 1.65	6.05 ± 1.13	0.0751	0.332
Triglyceride (mg/dL)	145.6 ± 71.9 [112]	127.9 ± 62.9	162.7 ± 76.4	0.0098	0.497
Total Cholesterol (mg/dL)	202.4 ± 37.8 [112]	208.7 ± 38.0	196.4 ± 36.8	0.0838	0.329
LDL Cholesterol (mg/dL)	118.0 ± 34.5 [112]	124.3 ± 35.5	112.0 ± 32.7	0.0585	0.360
HDL Cholesterol (mg/dL)	55.4 ± 15.6 [112]	58.8 ± 14.6	52.1 ± 15.9	0.0221	0.439
Glucose (mg/dL)	104.5 ± 22.5 [111]	102.2 ± 19.2	106.8 ± 25.3	0.2893	0.205
Hemoglobin A1c (NGSP) (%)	6.03 ± 0.83 [91]	5.89 ± 0.63	6.17 ± 0.97	0.1078	0.342
Hs-CRP (ng/mL)	473.0 (263.8–735.8) [110]	468.0 (199.0–702.0)	552.0 (281.5–950.5)	0.1965	0.408
UACR (mg/g Cre)	59.2 (19.3–191.35) [112]	42.1 (18.2–130.6)	82.0 (22.8–459.7)	0.0551	0.449
Primary cause of CKD					
Diabetic nephropathy (%)	11 (9.8) [112]	3 (5.5)	8 (14.0)	0.2036	0.290
Chronic glomerulonephritis (%)	49 (43.8) [112]	26 (47.3)	23 (40.4)	0.4604	0.139
Nephrosclerosis (%)	31 (27.7) [112]	14 (25.5)	17 (29.8)	0.6053	0.096
Others (%)	21 (18.8) [112]	12 (21.8)	9 (15.8)	0.4138	0.154
Concomitant drugs					
Antihypertensive agents (%)	78 (69.6) [112]	36 (65.5)	42 (73.7)	0.3437	0.179
ARB and or ACEI	59 (52.7) [112]	26 (47.3)	33 (57.9)	0.2603	0.213
CCB	34 (30.4) [112]	16 (29.1)	18 (31.6)	0.7747	0.054
Antidyslipidemic agents (n (%))	48 (42.9) [112]	16 (29.1)	32 (56.1)	0.0038	0.568
Antihyperuricemic agents (%)	45 (40.2) [112]	24 (43.6)	21 (36.8)	0.4634	0.139
Antidiabetic agents (%)	12 (10.7) [112]	3 (5.5)	9 (15.8)	0.1247	0.339
Corticosteroids (%)	8 (7.1) [112]	4 (7.3)	4 (7.0)	1.0000	0.012
Immunosuppressants (%)	6 (5.4) [112]	3 (5.5)	3 (5.3)	1.0000	0.009
Diuretics (%)	25 (22.3) [112]	16 (29.1)	9 (15.8)	0.0910	0.323
Comorbidities					
Hypertension (%)	77 (68.8) [112]	36 (65.5)	41 (71.9)	0.4598	0.138
Hyperuricemia (%)	55 (49.1) [112]	29 (52.7)	26 (45.6)	0.4516	0.142
Hypertriglyceridemia (%)	67 (59.8) [112]	26 (47.3)	41 (71.9)	0.0078	0.518
Hypercholesterolemia (%)	76 (67.9) [112]	35 (63.6)	41 (71.9)	0.3475	0.178
Low HDL cholesterol (%)	52 (46.4) [112]	16 (29.1)	36 (63.2)	0.0003	0.728
Hyperglycemia (%)	37 (33.0) [112]	15 (27.3)	22 (38.6)	0.2027	0.242
Diabetes mellitus (%)	21 (18.8) [112]	7 (12.7)	14 (24.6)	0.1087	0.309

*Continuous variables are expressed as means and standard deviations. Categorical variables are expressed as n (%). Values of nonmissing data are shown in [ ]. Abbreviations: Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; n, number; *P*, calculated probability; SD, standardized differences; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery; NA, not applicable; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; UACR, urine albumin-to-creatinine ratio; ARB, angiotensin Ⅱ receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium-channel blocker.

Table 2. Results of the univariate and the multivariate Cox analyses for the risk factors associated with disease progression (i.e., a ≥ 30% estimated glomerular filtration rate decline or end-stage renal disease) among the entire study population (n = 112)

Variables	Univiate arAnalysis		Multivariate Analysis for Max bulb-IMT (n = 88)			Multivariate Analysis for Max ICA-IMT (n = 82)			Multivariate Analysis for Max IMT (n = 112)		
	Hazard Ratio (95% CI)	*P*-Value	Hazard Ratio (95% CI)	*P*-Value	*P*-INT	Hazard Ratio (95% CI)	*P*-Value	*P*-INT	Hazard Ratio (95% CI)	*P*-Value	*P*-INT
Age (1 year increase)	1.04 (1.00–1.07)	0.0343	0.98 (0.91–1.07)	0.7144	0.0692	0.96 (0.88–1.03)	0.2572	0.1184	0.98 (0.92–1.05)	0.6323	0.0407
Men (vs. women)	1.27 (0.70–2.38)	0.4335	0.64 (0.25–1.63)	0.3517	0.0907	0.55 (0.23–1.30)	0.1718	0.6309	0.70 (0.31–1.57)	0.3907	0.0689
eGFR (10 mL/min/1.73 m^2 increase)	0.64 (0.53–0.76)	<0.0001	0.64 (0.51–0.79)	<0.0001	0.3818	0.67 (0.54–0.83)	0.0001	0.6228	0.65 (0.53–0.79)	<0.0001	0.5309
UACR (10 mg/g Cre increase)	1.01 (1.01–1.02)	<0.0001	1.01 (1.01–1.02)	0.0003	0.1068	1.01 (1.01–1.02)	0.0009	0.1920	1.01 (1.01–1.02)	0.0005	0.1247
Max CCA-IMT (1 mm increase)	1.02 (0.58–1.59)	0.9338	-	-	-	-	-	-	-	-	-
Max bulb-IMT (1 mm increase) [88]	1.27 (0.88–1.79)	0.2493	1.82 (1.15–2.89)	0.0103	0.1066	-	-	-	-	-	-
Max ICA-IMT 1 mm increase) [82]	1.27 (0.93–1.67)	0.1267	-	-	-	1.57 (1.02–2.38)	0.0409	0.0490	-	-	-
Max IMT (1 mm increase)	1.42 (1.07–1.83)	0.0151	-	-	-	-	-	-	1.65 (1.14–2.36)	0.0084	0.0153

Values of nonmissing data are shown in [ ]. Variables of IMT, as well as age, sex, eGFR, and interaction terms (all variables * age ≥ 65 years), were included in the multivariate model. Regarding IMT in the multivariate model, we assessed four types of IMT: Max IMT (1 mm increase); Max CCA-IMT (1 mm increase); Max bulb-IMT (1 mm increase); Max ICA-IMT (1 mm increase). Abbreviations: *n*, number; CI, confidence interval; *P*, calculated probability; *P*-INT, *P*-value for interaction; vs., versus; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; Cre, creatinine; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery; Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries.

eGFR, and interaction terms of interest (variables with a *P*-Value for interaction <0.1 in the **Table 2** * age ≥ 65 years) **(Supplementary Table 4)**.

Results of the multivariate Cox regression analyses according to age-based sub-cohort (age <65 years and age ≥ 65 years) are provided in **Table 3**. In patients with age <65 years, disease progression was significantly associated with 1-mm increase in Max IMT, Max bulb-IMT, and Max ICA-IMT. In contrast, no significant association was observed between Max CCA-IMT and kidney disease progression. On the other hand, in patients with age ≥ 65 years, disease progression was not significantly associated with all Max IMTs. Importantly, there was statistical heterogeneity in CKD progression for Max IMT (1-mm increase), and the hazard ratio (HR) of Max IMT (1-mm increase) was higher in the sub-cohort with age <65 years than in the sub-cohort with age ≥ 65 years (HR: 2.52 vs. 0.95) **(Fig. 1A)**. Similar results were obtained for Max bulb-IMT (HR: 3.05 vs. 1.22) **(Fig. 1C)**, Max ICA-IMT (HR: 2.20 vs. 0.94) **(Fig. 1D)**, but not for Max CCA-IMT (HR: 0.96 vs. 0.84) **(Fig. 1B)**.

Kaplan–Meier analyses with eGFR decline ≥ 30% or ESRD as the endpoint, showed that the kidney survival rate was significantly lower in the high Max IMT group (≥ 1.5 mm) than in the low Max IMT group (<1.5 mm) **(Fig. 2A)**. Even after adjusting for age, sex, hemoglobin A1c, and eGFR in the propensity score-matched cohort, the kidney survival rate remained significantly lower in the high Max IMT group (≥ 1.5 mm) than in the low Max IMT group (<1.5 mm), **(Fig. 2B)**.

Discussion

Recently, patient-centered medicine has been advocated[23, 24]. For patient-centered medicine application, it is necessary to treat individual patients according to their heterogeneous characteristics[25]. The

Table 3. Results of the multivariate Cox analyses for the risk factors associated with disease progression (i.e., a ≥ 30% estimated glomerular filtration rate decline or end-stage renal disease) according to age-based sub-cohort (age < 65 years and age ≥ 65 years)

Variables	Multivariate Analysis (Total)		Multivariate Analysis (Age < 65 years)		Multivariate Analysis (Age ≥ 65 years)	
	Hazard Ratio (95% CI)	*P*-Value	Hazard Ratio (95% CI)	*P*-Value	Hazard Ratio (95% CI)	*P*-Value
Model 1 for Max IMT	(*n* = 112)		(*n* = 64)		(*n* = 48)	
Age (1 year increase)	0.99 (0.96–1.03)	0.7602	0.92 (0.84–1.01)	0.0905	1.06 (0.95–1.18)	0.2998
Men (vs. women)	0.74 (0.35–1.56)	0.4225	0.35 (0.11–1.06)	0.0630	1.47 (0.44–4.86)	0.5252
eGFR (10 mL/min/1.73 m^2 increase)	0.65 (0.54–0.79)	< 0.0001	0.60 (0.44–0.79)	0.0002	0.72 (0.55–0.94)	0.0176
UACR (10 mg/g Cre increase)	1.01 (1.01–1.01)	0.0004	1.02 (1.01–1.03)	0.0058	1.01 (1.00–1.02)	0.0030
Max IMT (1 mm increase)	1.47 (1.02–2.08)	0.0393	2.52 (1.48–4.22)	0.0011	0.95 (0.57–1.58)	0.8545
Model 2 for Max CCA-IMT	(*n* = 112)		(*n* = 64)		(*n* = 48)	
Age (1 year increase)	1.01 (0.98–1.05)	0.5564	0.98 (0.90–1.07)	0.6024	1.06 (0.95–1.17)	0.3195
Men (vs. women)	1.04 (0.52–2.11)	0.9141	0.73 (0.27–1.92)	0.5243	1.57 (0.50–4.92)	0.4402
eGFR (10 mL/min/1.73 m^2 increase)	0.68 (0.56–0.81)	< 0.0001	0.64 (0.48–0.84)	0.0014	0.71 (0.54–0.94)	0.0107
UACR (10 mg/g Cre increase)	1.01 (1.00–1.01)	0.0003	1.02 (1.00–1.03)	0.0121	1.01 (1.00–1.01)	0.0073
Max CCA-IMT (1 mm increase)	1.02 (0.59–1.59)	0.9281	0.96 (0.31–2.50)	0.9410	0.84 (0.43–1.66)	0.6045
Model 3 for Max bulb-IMT	(*n* = 88)		(*n* = 48)		(*n* = 40)	
Age (1 year increase)	1.00 (0.96–1.04)	0.9105	0.92 (0.82–1.04)	0.1943	1.05 (0.94–1.17)	0.3862
Men (vs. women)	0.76 (0.33–1.75)	0.5155	0.26 (0.05–1.06)	0.0599	1.20 (0.37–4.27)	0.7666
eGFR (10 mL/min/1.73 m^2 increase)	0.63 (0.51–0.77)	< 0.0001	0.54 (0.36–0.76)	0.0003	0.72 (0.55–0.93)	0.0125
UACR (10 mg/g Cre increase)	1.01 (1.01–1.02)	0.0004	1.02 (1.01–1.03)	0.0037	1.01 (1.00–1.01)	0.0061
Max bulb-IMT (1 mm increase)	1.65 (0.99–2.56)	0.0525	3.05 (1.42–5.93)	0.0079	1.22 (0.61–2.32)	0.5636
Model 4 for Max ICA-IMT	(*n* = 82)		(*n* = 5)		(*n* = 37)	
Age (1 year increase)	0.99 (0.96–1.03)	0.6738	0.91 (0.81–1.01)	0.0840	1.02 (0.91–1.14)	0.7241
Men (vs. women)	0.71 (0.34–1.51)	0.3715	0.47 (0.14–1.55)	0.2139	0.67 (0.19–2.34)	0.5271
eGFR (10 mL/min/1.73 m^2 increase)	0.67 (0.54–0.81)	< 0.0001	0.63 (0.46–0.84)	0.0016	0.73 (0.54–0.98)	0.0369
UACR (10 mg/g Cre increase)	1.01 (1.00–1.01)	0.0010	1.02 (1.00–1.03)	0.0149	1.01 (1.00–1.02)	0.0048
Max ICA-IMT (1 mm increase)	1.25 (0.86–1.73)	0.2300	2.20 (1.18–4.15)	0.0147	0.94 (0.46–1.60)	0.8517

Variables of IMT, as well as age, sex, eGFR, and UACR, were included in the multivariate model. Regarding IMT in the multivariate model, we assessed four types of IMT: Model 1, Max IMT (1 mm increase); Model 2, Max CCA-IMT (1 mm increase); Model 3, Max bulb-IMT (1 mm increase); Model 4, Max ICA-IMT (1 mm increase). Abbreviations: CI, confidence interval; *P*, calculated probability; *n*, number; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; Cre, creatinine; Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery.

development of patient-centered medicine requires disaggregation of data and analysis of differences in subgroups[26, 27].

There are two main findings in the present study. Firstly, an association between Max IMT and renal outcomes was confirmed for the first time in a cohort exclusively consisting of patients with CKD, as well as in a cohort matched for age, sex, hemoglobin A1c, and eGFR. Secondly, Max IMT showed a significant interaction with age category (age ≥ 65 years) with regard to the renal prognosis. As a result, there were differences in the renal prognostic factors between the two age-based sub-cohorts (age ≥ 65 years and age < 65 years). One of the reasons we were able to detect an association between Max IMT and renal outcomes in the present study may be the follow-up duration. Previous studies that reported an association between carotid IMT and renal function decline in diabetic patients (two studies)[15, 16], and the general population[17], had median follow-up durations of 6.0 years, 10.8 years, and 22.7 years, respectively. The median follow-up period of 12.5 years in the present study was comparable to these previous studies. The independent association between Max IMT and CKD progression observed in long-term follow-up studies may be because of the stability of Max IMT as a renal

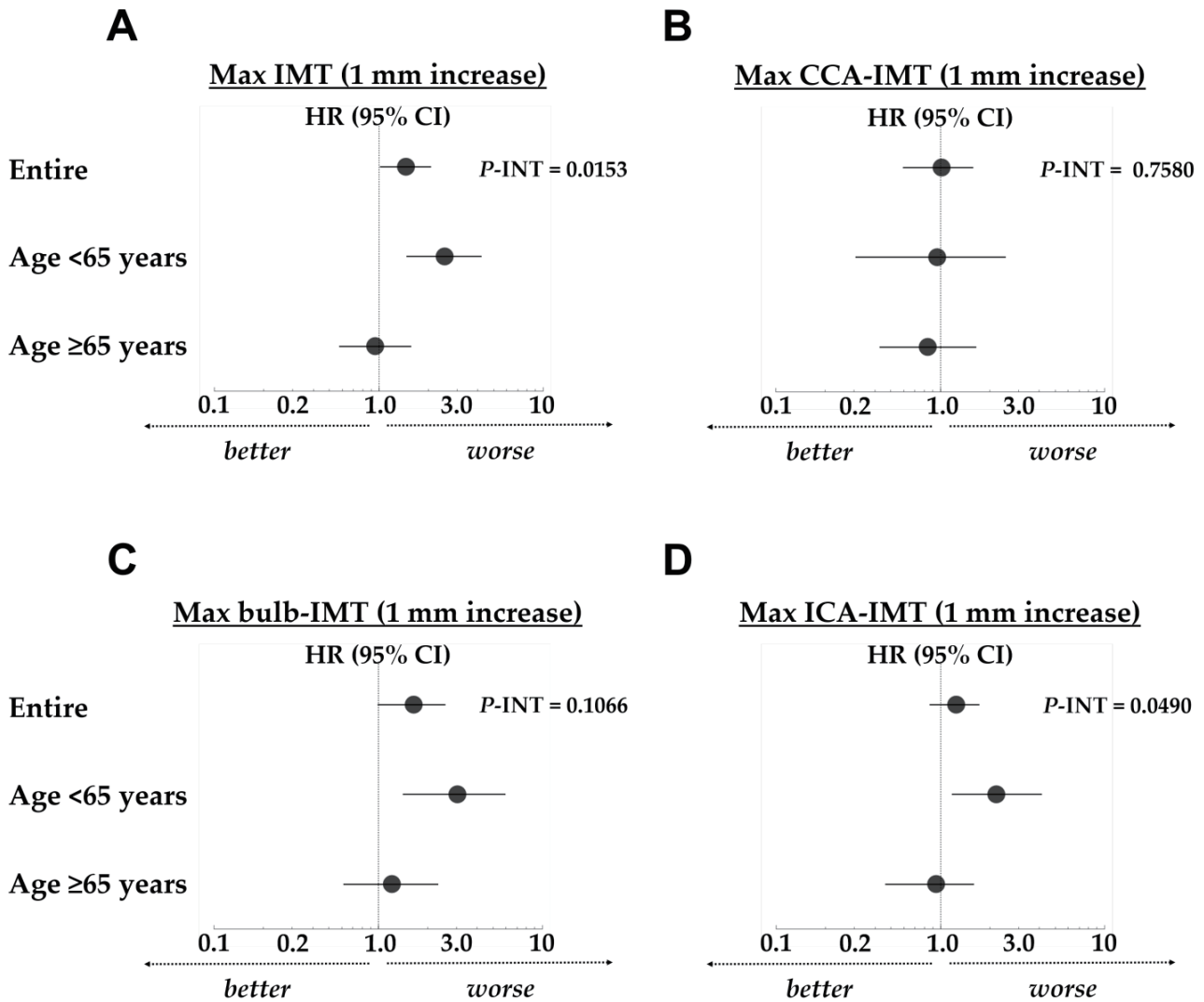

Fig. 1. Hazard ratios for renal prognosis derived from the multivariate Cox proportional hazards analyses

(A) Max IMT; (B) Max CCA-IMT; (C) Max bulb-IMT; (D) Max ICA-IMT. The circles represent HRs and the bars represent 95% CI for the association with renal prognosis, with an eGFR decline ≥ 30% or ESRD as the endpoint (derived from Table 3). The *P*-value for the interaction is derived from the multivariate Cox analyses including interaction terms (all variables * age ≥ 65 years) for the entire study population in Table 2.

Abbreviations: Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery; HR, hazard ratio; CI, confidence interval; *P*-INT, *P*-value for the interaction; *P*, calculated probability; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

risk factor over time.

The measurement of the arterial wall using B-mode ultrasound has improved the early identification of patients with CKD who are prone to developing atherosclerosis. However, until recently, whether carotid IMT is useful in predicting the progression of kidney disease was not clarified[14]. Generally, CKD is multifactorial[27], and its progression is associated with various risk factors linked to atherosclerosis, such as hypertension[28], diabetes mellitus, dyslipidemia[29], obesity, and metabolic syndrome[30]. Interpreting the results of clinical studies can sometimes be challenging, as these factors complicatedly affect one another. Indeed, as we recently reported[27], renal prognosis analyses are strongly influenced by the factors examined and the cohort analyzed. Therefore, the usefulness of IMT measurements for renal prognosis may change depending on the variable examined (ICA-

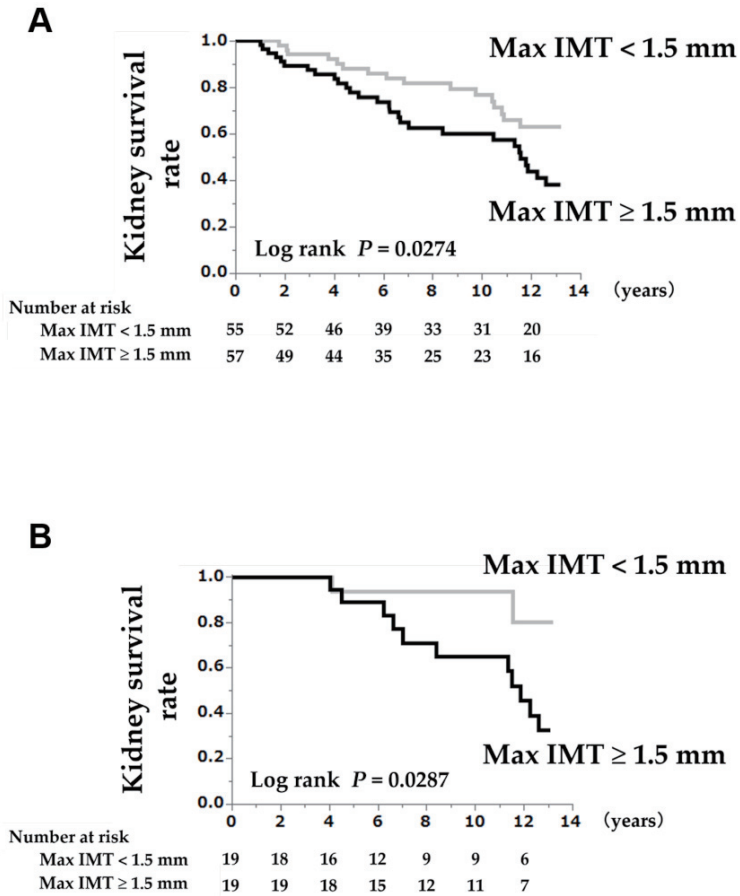

Fig. 2. Kidney survival rates, with an eGFR decline ≥ 30% or ESRD as the endpoint

(A) Kidney survival rates in the high Max IMT group (≥ 1.5 mm) and low Max IMT group (<1.5 mm) for the entire cohort. The renal prognosis for patients with Max IMT ≥ 1.5 mm was poor. (B) Kidney survival rates in the high Max IMT group (≥ 1.5 mm) and the low Max IMT group (<1.5 mm) for the propensity score-matched cohort. The renal prognosis for patients with Max IMT ≥ 1.5 mm was poor, even after matching the groups in terms of age, sex, hemoglobin A1c, and estimated glomerular filtration rate.
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; *P*, calculated probability.

IMT or CCA-IMT) and the cohort evaluated (young or elderly).

The results of the present study provide meaningful information, as the association between Max IMT and CKD progression remained significant after propensity matching for age, sex, hemoglobin A1c, and eGFR, suggesting an independent contribution of Max IMT to the progression of CKD. In contrast, Max CCA-IMT was not associated with renal prognosis. ICA-IMT and CCA-IMT are the two major IMT types commonly evaluated. Polak *et al.*[6] suggested that these two IMT types likely represent separate phenotypes, since their patterns of associations with risk factors are different[1, 7, 8, 31]. Thus, further evaluation of the role of ICA-IMT is required. Previous research showed that the ICA-IMT has a qualitatively stronger association with low-density lipoprotein cholesterol[7], as well as stronger associations with coronary heart disease events[1, 8, 31], than does CCA-IMT. Nevertheless, attempts to determine the diagnostic significance of the IMT formerly focused on CCA-IMT and not on ICA-IMT[32]. Additionally, the American College of Cardiology/American Heart Association Work Group recommended against measuring carotid IMT as routine clinical practice for risk assessment in a first atherosclerotic CVD event, based on the evidence regarding CCA-IMT provided by Ruijter *et al.*[33-35]. However, there is still a possibility that ICA-IMT or the combination of CCA-IMT and ICA-IMT may add incremental value to traditional risk factors for predicting CVD[6] or CKD progression. Although the present study is observational in nature, we found an association between CKD progression and Max IMT which may imply a close relationship between CKD

progression and coronary heart disease[36].

Considering that increased IMT is associated with age[16, 17], studies that evaluate its interaction with age (young or elderly) are desired. In the present study, we found an interaction between Max IMT and age category (age ≥ 65 years), and the HR of Max IMT (1-mm increase) was higher in the sub-cohort with age <65 years than in the sub-cohort with age ≥ 65 years (HR: 2.52 vs. 0.95). In a previous study on CVD, O'Leary *et al.* cross-sectionally measured ICA-IMT in elderly patients (age ≥ 65 years) and found that ICA-IMT was associated with existing coronary heart disease[8]. O'Leary and colleagues also reported that increased ICA-IMT is directly associated with an increased risk of myocardial infarction and stroke in individuals age ≥ 65 years and without a history of CVD[31]. Generally, as reported in these studies, elderly people develop advanced arteriosclerosis and are more prone to cardiovascular events[37].

On the other hand, although the results of studies on elderly status as a renal prognostic factor in patients with CKD are inconsistent[38], the Chronic Renal Insufficiency Cohort Study in the United States reported that older age (age ≥ 65 years) is associated with a lower rate of ESRD (age >65 vs. <45 years: HR, 0.55)[39]. The finding that Max IMT significantly interacted with age category (age ≥ 65 years or <65 years) with regard to renal prognosis is consistent with previous reports on pathophysiological differences between elderly and younger adult patients with CKD[40, 41]. Furthermore, the finding of a higher HR of Max IMT (1-mm increase) in terms of renal prognosis in patients aged <65 years than in patients aged ≥ 65 years is meaningful from a preventive perspective. Considering that elderly patients with CKD have complex pathophysiology, IMT as a screening tool may be suitable for younger patients with CKD.

This study has several limitations. First, although data of IMTs were obtained by experienced and centrally-trained vascular sonographer specialists, we did not assess the intra-observer and inter-observer variability. Therefore, the presence of some systematic measurement error cannot be ruled out. Second, the impact of subsequent Max IMT changes on outcomes could not be demonstrated because only baseline laboratory data were analyzed. Third, the serum creatinine level was based on a single assessment at baseline, which may have been influenced by existing comorbidities at the time of the assessment. Fourth, a potential selection bias was unavoidable because patients voluntarily enrolled in this study. Fifth, since all the participants were Japanese patients with CKD, the association between Max IMTs and renal outcomes may not be generalizable to other populations. Sixth, the study was observational in nature; thus, the observed associations do not prove causality, and residual confounding due to unmeasured or unknown factors cannot be ruled out. On the other hand, the strengths of the present study include its well-characterized population of Japanese patients with CKD who were treated by nephrologists at a single center using standard CKD care guidelines and the detailed analyses that were designed to disaggregate the data based on Max IMTs, which is significant for achieving patient-centered medicine[23, 24].

5. Conclusions

Max IMT ≥ 1.5 mm was significantly associated with renal prognosis in patients with CKD, confirmed by age- and eGFR-matched cohort analysis. Importantly, a higher Max IMT/Max bulb-IMT/Max ICA-IMT was a significant factor for renal prognosis in patients with CKD aged <65 years. Our results may provide new insights into treating CKD.

Declaration of Competing Interest

None.

Financial Support

None.

Author Contributions

Conceptualization: S.M. (Shun Manabe), H.K., and T.M.; data curation: S.M. (Shun Manabe), H.K., T.M., Y.U., K.K., K.W., S.W., T.A., S.M. (Shiho Makabe), N.I., M.S., R.Y., and Y.S.; formal analysis: S.M. (Shun Manabe) and H.K.; supervision: K.I., N.H., T.M., K.T., and K.N. All authors contributed important intellectual content during manuscript drafting or revision, accept personal accountability for their own contributions, and agree to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

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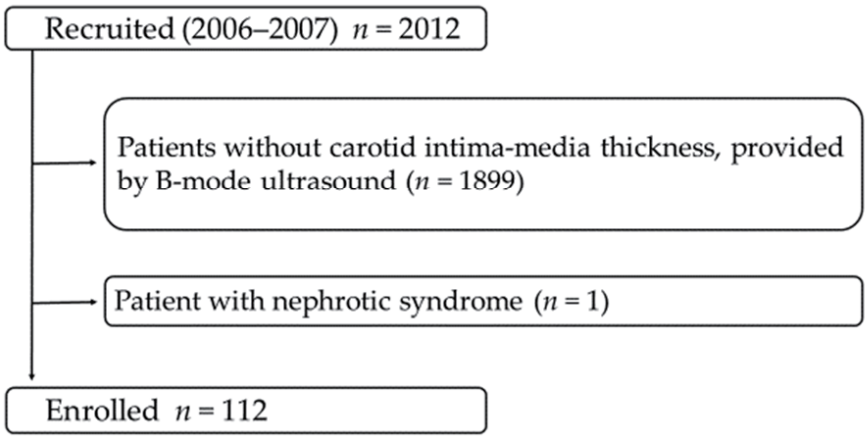

Supplementary Fig. 1. Patient selection flow chart

The patient selection flowchart is shown. Among 2012 screened patients, 1899 patients without B-mode ultrasound data, and 1 patient with nephrotic syndrome were excluded from the study. The remaining 112 patients were enrolled.

Supplementary Methods

Definitions of Comorbidities and Primary Causes of CKD

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or taking an antihypertensive agent. Hyperuricemia was defined as serum UA level ≥ 7.0 mg/dL or taking an antihyperuricemic agent. Hyperglycemia was defined as blood glucose ≥ 100 mg/dL. DM was defined as glycated hemoglobin level ≥ 6.5%, diagnosis of DM, or intake of an antidiabetic agent. Hypertriglyceridemia was defined as a serum TG level ≥ 150 mg/dL or intake of an oral lipid-lowering agent. Hypercholesterolemia was defined as serum total cholesterol level ≥ 220 mg/dL, serum LDL cholesterol level ≥ 140 mg/dL, or intake of an oral lipid-lowering agent. Low HDL cholesterol was defined as a serum HDL cholesterol level ≤ 40 mg/dL among men and ≤ 50 mg/dL among women. Diabetic kidney disease, chronic glomerulonephritis, and nephrosclerosis were diagnosed either from biopsies or clinically by the doctor in charge.

Supplementary Table 1. Patient characteristics according to the levels of the maximum intima–media thickness of the carotid artery (Propensity score matched cohort: $n = 38$)

Variables	Entire Cohort	Max IMT < 1.5 mm	Max IMT ≥ 1.5 mm	*P*-Value	*SD*
	$n = 38$	$n = 19$	$n = 19$		
Clinical Findings					
Age (years)	62.2 ± 9.2 [38]	61.8 ± 10.4	62.5 ± 8.2	0.8098	0.075
Gender (Men; %)	28 (73.7) [38]	14 (73.7)	14 (73.7)	1.0000	0.000
SBP (mmHg)	126.0 ± 7.1 [38]	125.6 ± 6.9	126.3 ± 7.4	0.7821	0.098
DBP (mmHg)	77.6 ± 5.4 [38]	77.6 ± 4.3	77.5 ± 6.5	0.9454	0.018
MBP (mmHg)	93.7 ± 5.8 [38]	93.6 ± 5.1	93.8 ± 6.5	0.9438	0.034
BMI (kg/m^2)	25.1 ± 3.6 [38]	25.0 ± 3.3	25.3 ± 3.9	0.8210	0.083
Max CCA-IMT (mm)	0.9 (0.7–1.3) [38]	0.8 (0.7–1.1)	0.9 (0.8–1.8)	0.0378	0.819
Max bulb-IMT (mm)	1.2 (0.9–1.9) [30]	1.0 (0.9–1.3)	1.8 (1.1–2.4)	0.0028	1.176
Max ICA-IMT (mm)	1.8 (1.2–2.5) [25]	1.2 (1.1–1.3)	2.1 (1.7–3.4)	0.0024	1.415
Max IMT (mm)	1.5 (1.2–2.4) [38]	1.2 (0.9–1.3)	2.4 (1.9–3.3)	< 0.0001	2.026
Distribution ratio of Max-IMT: CCA/ bulb /ICA	6 (15.8)/ 13 (34.2)/ 19 (50.0)	4 (21.1)/ 9 (47.4)/ 6 (31.6)	2 (10.5)/ 4 (21.1)/ 13 (68.4)	0.0754	NA
Laboratory Findings					
Serum Albumin (g/dL)	4.23 ± 0.30 [38]	4.17 ± 0.33	4.29 ± 0.26	0.2174	0.404
Hemoglobin (g/dL)	14.1 ± 1.5 [38]	14.1 ± 1.7	14.2 ± 1.3	0.9573	0.066
Serum Creatinine (mg/dL)	0.97 ± 0.24 [38]	0.97 ± 0.25	0.97 ± 0.24	0.9372	0.000
eGFR ($mL/min/1.73\ m^2$)	61.0 ± 16.7 [38]	61.3 ± 16.5	60.7 ± 17.3	0.9133	0.035
CKD stage 1/ 2/ 3a/3b/4/5 (%)	2 (5.3)/ 15 (39.5)/ 16 (42.1)/ 5 (13.2)/ 0 (0.0)/ 0 (0.0)	1 (5.3)/ 7 (36.8)/ 9 (47.4)/ 2 (10.5)/ 0 (0.0)/ 0 (0.0)	1 (5.3)/ 8 (42.1)/ 7 (36.8)/ 3 (15.8)/ 0 (0.0)/ 0 (0.0)	0.9152	NA
Uric Acid (mg/dL)	6.17 ± 1.28 [38]	6.22 ± 1.48	6.11 ± 1.08	0.7935	0.085
Triglyceride (mg/dL)	141.3 ± 64.0 [38]	125.1 ± 55.2	157.5 ± 69.4	0.1203	0.517
Total Cholesterol (mg/dL)	207.3 ± 33.9 [38]	202.6 ± 31.7	211.9 ± 36.2	0.4069	0.273
LDL Cholesterol (mg/dL)	123.8 ± 33.8 [38]	120.6 ± 35.0	127.0 ± 33.2	0.5631	0.188
HDL Cholesterol (mg/dL)	55.6 ± 12.9 [38]	57.1 ± 12.5	54.2 ± 13.5	0.4979	0.223
Glucose (mg/dL)	108.6 ± 27.7 [38]	112.1 ± 24.6	105.0 ± 30.7	0.4366	0.255
Hemoglobin A1c (NGSP) (%)	6.05 ± 0.69 [38]	6.11 ± 0.78	5.99 ± 0.59	0.6265	0.174
Hs-CRP (ng/mL)	412.0 (246.0–680.5) [37]	473.0 (301.3–714.0)	402.0 (219.0–620.0)	0.5740	0.166
UACR (mg/g Cre)	40.3 (18.0–148.3) [38]	42.1 (18.6–150.4)	34.8 (17.5–147.0)	0.8040	0.253
Primary cause of CKD					
Diabetic nephropathy (%)	2 (5.3) [38]	1 (5.3)	1 (5.3)	1.0000	0.000
Chronic glomerulonephritis (%)	18 (47.4) [38]	7 (36.8)	11 (57.9)	0.3300	0.432
Nephrosclerosis (%)	12 (31.6) [38]	8 (42.1)	4 (21.1)	0.2953	0.464
Others (%)	6 (15.8) [38]	3 (15.8)	3 (15.8)	1.0000	0.000
Concomitant drugs					
Antihypertensive agents (%)	26 (68.4) [38]	12 (63.2)	14 (73.7)	0.7281	0.227
ARB and or ACEI	18 (47.4) [38]	8 (42.1)	10 (52.6)	0.7459	0.211
CCB	9 (23.7) [38]	4 (21.1)	5 (26.3)	1.0000	0.123
Antidyslipidemic agents (*n* (%))	16 (42.1) [38]	7 (36.8)	9 (47.4)	0.7431	0.216
Antihyperuricemic agents (%)	17 (44.7) [38]	12 (63.2)	5 (26.3)	0.0489	0.799
Antidiabetic agents (%)	5 (13.2) [38]	2 (10.5)	3 (15.8)	1.0000	0.157
Corticosteroids (%)	5 (13.2) [38]	3 (15.8)	2 (10.5)	1.0000	0.157
Immunosuppressants (%)	3 (7.9) [38]	2 (10.5)	1 (5.3)	1.0000	0.194
Diuretics (%)	9 (23.7) [38]	5 (26.3)	4 (21.1)	1.0000	0.123
Comorbidities					
Hypertension (%)	26 (68.4) [38]	12 (63.2)	14 (73.7)	0.7281	0.227
Hyperuricemia (%)	22 (57.9) [38]	14 (73.7)	8 (42.1)	0.0991	0.676
Hypertriglyceridemia (%)	22 (57.9) [38]	9 (47.4)	13 (68.4)	0.3245	0.435
Hypercholesterolemia (%)	25 (65.8) [38]	10 (52.6)	15 (79.0)	0.1704	0.579
Low HDL cholesterol (%)	18 (47.4) [38]	7 (36.8)	11 (57.9)	0.3300	0.432
Hyperglycemia (%)	22 (57.9) [38]	14 (73.7)	8 (42.1)	0.0991	0.676
Diabetes mellitus (%)	8 (21.1) [38]	4 (21.1)	4 (21.1)	1.0000	0.000

*Continuous variables are expressed as means and standard deviations. Categorical variables are expressed as *n* (%). Values of nonmissing data are shown in [ ]. Abbreviations: Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; *n*, number; *P*, calculated probability; SD, standardized differences; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery; NA, not applicable; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; UACR, urine albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium-channel blocker.

Supplementary Table 2. Patient characteristics of the entire cohort and of subcohorts stratified by age

Variables	Entire Cohort	Age < 65	Age ≥ 65	*P*-Value
	n = 112	*n* = 64	*n* = 48	
Clinical Findings				
Age (years)	63.0 ± 10.3 [112]	55.6 ± 6.4	72.9 ± 4.7	< 0.0001
Gender (Men; %)	66 (58.9) [112]	36 (56.3)	30 (62.5)	0.5058
SBP (mmHg)	126.2 ± 6.7 [112]	126.1 ± 7.2	126.3 ± 5.9	0.9105
DBP (mmHg)	77.4 ± 5.0 [112]	77.7 ± 5.4	76.9 ± 4.5	0.4244
MBP (mmHg)	93.6 ± 5.4 [112]	93.8 ± 6.0	93.4 ± 4.5	0.6492
BMI (kg/m^2)	24.5 ± 3.4 [112]	24.9 ± 3.6	23.9 ± 3.1	0.1076
Max CCA-IMT (mm)	0.9 (0.8–1.3) [112]	0.9 (0.7–1.2)	1.1 (0.8–1.4)	0.0093
Max bulb-IMT (mm)	1.2 (0.9–1.7) [88]	1.1 (0.9–1.6)	1.4 (1.0–2.1)	0.0242
Max ICA-IMT (mm)	1.6 (1.2–2.4) [82]	1.3 (1.1–2.0)	1.8 (1.3–2.9)	0.0330
Max IMT (mm)	1.5 (1.2–2.2) [112]	1.2 (0.9–2.0)	1.8 (1.4–2.9)	0.0007
Distribution ratio of Max-IMT: CCA/ bulb /ICA	18 (16.1)/ 38 (33.9)/ 56 (50.0) [112]	12 (18.8)/ 23 (35.9)/ 29 (45.3)	6 (12.5)/ 15 (31.3)/ 27 (56.3)	0.4722
Laboratory Findings				
Serum Albumin (g/dL)	4.22 ± 0.28 [112]	4.32 ± 0.26	4.10 ± 0.27	< 0.0001
Hemoglobin (g/dL)	13.5 ± 1.7 [112]	14.1 ± 1.6	12.6 ± 1.6	< 0.0001
Serum Creatinine (mg/dL)	1.18 ± 0.82 [112]	1.07 ± 0.60	1.32 ± 1.03	0.1016
eGFR (mL/min/1.73 m^2)	56.0 ± 20.6 [112]	59.4 ± 18.9	51.5 ± 22.1	0.0429
CKD stage 1/ 2/ 3a/3b/4/5 (%)	5 (4.5)/ 40 (35.7)/ 37 (33.0)/ 16 (14.3)/ 10 (8.9)/ 4 (3.6) [112]	3 (4.7)/ 28 (43.8)/ 20 (31.3)/ 7 (10.9)/ 5 (7.8)/ 1 (1.6)	2 (4.2)/ 12 (25.0)/ 17 (35.4)/ 9 (18.8)/ 5 (10.4)/ 3 (6.3)	0.3132
Uric Acid (mg/dL)	5.82 ± 1.42 [112]	5.77 ± 1.50	5.89 ± 1.33	0.6735
Triglyceride (mg/dL)	145.6 ± 71.9 [112]	147.7 ± 79.4	142.9 ± 61.2	0.7301
Total Cholesterol (mg/dL)	202.4 ± 37.8 [112]	209.0 ± 36.9	193.7 ± 37.5	0.0333
LDL Cholesterol (mg/dL)	118.0 ± 34.5 [112]	123.5 ± 34.4	110.8 ± 33.7	0.0529
HDL Cholesterol (mg/dL)	55.4 ± 15.6 [112]	6.2 ± 13.8	54.4 ± 17.8	0.5417
Glucose (mg/dL)	104.5 ± 22.5 [111]	105.1 ± 24.8	103.7 ± 19.3	0.7585
Hemoglobin A1c (NGSP) (%)	6.03 ± 0.83 [91]	6.01 ± 0.74	6.06 ± 0.96	0.7638
Hs-CRP (ng/mL)	473.0 (263.8–735.8) [110]	385.5 (197.0–626.8)	630.5 (398.5–933.8)	0.0021
UACR (mg/g Cre)	59.2 (19.3–191.3) [112]	56.6 (18.5–182.2)	61.2 (21.6–239.9)	0.5805
Primary cause of CKD				
Diabetic nephropathy (%)	11 (9.8) [112]	5 (7.8)	6 (12.5)	0.5250
Chronic glomerulonephritis (%)	49 (43.8) [112]	28 (43.8)	21 (43.8)	1.0000
Nephrosclerosis (%)	31 (27.7) [112]	17 (26.6)	14 (29.2)	0.7605
Others (%)	21 (18.8) [112]	14 (21.9)	7 (14.6)	0.4637
Concomitant drugs				
Antihypertensive agents (%)	78 (69.6) [112]	44 (68.8)	34 (70.8)	0.8124
ARB and or ACEI	59 (52.7) [112]	34 (53.1)	25 (52.1)	0.9130
CCB	34 (30.4) [112]	17 (26.6)	17 (35.4)	0.3132
Antidyslipidemic agents (*n* (%))	48 (42.9) [112]	24 (37.5)	24 (50.0)	0.1859
Antihyperuricemic agents (%)	45 (40.2) [112]	28 (43.8)	17 (35.4)	0.3734
Antidiabetic agents (%)	12 (10.7) [112]	6 (9.4)	6 (12.5)	0.7592
Corticosteroids (%)	8 (7.1) [112]	4 (6.3)	4 (8.3)	0.7227
Immunosuppressants (%)	6 (5.4) [112]	3 (4.7)	3 (6.3)	1.0000
Diuretics (%)	25 (22.3) [112]	18 (28.1)	7 (14.6)	0.0885
Comorbidities				
Hypertension (%)	77 (68.8) [112]	44 (68.8)	33 (68.8)	1.0000
Hyperuricemia (%)	55 (49.1) [112]	33 (51.6)	22 (45.8)	0.5484
Hypertriglyceridemia (%)	67 (59.8) [112]	36 (56.3)	31 (64.6)	0.3734
Hypercholesterolemia (%)	76 (67.9) [112]	44 (68.8)	32 (66.7)	0.8153
Low HDL cholesterol (%)	53 (47.3) [112]	27 (42.2)	26 (54.2)	0.2089
Hyperglycemia (%)	58 (51.8) [112]	31 (48.4)	27 (56.3)	0.4129
Diabetes mellitus (%)	21 (18.8) [112]	11 (17.2)	10 (20.8)	0.6339

*Continuous variables are expressed as means and standard deviations. Categorical variables are expressed as *n* (%). Values of nonmissing data are shown in [ ]. Abbreviations: Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries; *n*, number; *P*, calculated probability; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index; Max CCA-IMT, maximum intima–media thickness of the common carotid artery; Max bulb-IMT, maximum intima–media thickness of the carotid bulb; Max ICA-IMT, maximum intima–media thickness of the internal carotid artery; NA, not applicable; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; UACR, urine albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium-channel blocker.

Supplementary Table 3. Results of the univariate and the multivariate linear regression analyses for the factors associated with baseline maximum carotid intima-media thickness among the entire cohort (n=122)

Variables	Univariate Analysis		Multivariate Analysis	
	β	P-Value	β	P-Value
Age (years)	0.35	0.0002	0.32	0.0003
Men (vs Women)	0.36	0.0001	0.30	0.0013
MBP (mmHg)	0.09	0.3229		
BMI (kg/m^2)	0.01	0.8766		
eGFR (mL/min/1.73 m^2)	-0.07	0.4936	0.10	0.2721
Uric acid (mg/dL)	0.11	0.2626		
Triglyceride (mg/dL)	0.10	0.2932		
HDL cholesterol (mg/dL)	-0.19	0.0483	0.09	0.2910
Glucose (mg/dL)	0.02	0.8455		
Hemoglobin A1c (NGSP) (%)	-0.01	0.8951		
Hs-CRP (ng/mL)	0.36	0.0001	0.23	0.0075
UACR (mg/g Cre)	0.16	0.0824	0.06	0.5047

*Variables with a P-value <0.1 in the univariate model, as well as age, sex, and eGFR, were included in the multivariate model. Abbreviations: n, number; β, standardized partial regression coefficient; P, calculated probability; MBP, mean blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; UACR, urine albumin-to-creatinine ratio; Cre, creatinine.

Supplementary Table 4. Results of the univariate and the multivariate Cox analyses for the risk factors associated with disease progression (i.e., a ≥ 30% estimated glomerular filtration rate decline or end-stage renal disease) among the entire study population (n=112)

Variables	Univariate Analysis		Multivariate Analysis		P-Value for interaction
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	
Age (1 year increase)	1.04 (1.00–1.07)	0.0343	0.98 (0.91–1.05)	0.5249	0.0423
Men (vs. women)	1.27 (0.70–2.38)	0.4335	0.83 (0.37–1.83)	0.6505	0.3245
eGFR (10 mL/min/1.73 m^2 increase)	0.64 (0.53–0.76)	<0.0001	0.70 (0.56–0.87)	0.0010	-
UACR (10 mg/g Cre increase)	1.01 (1.01–1.02)	<0.0001	1.01 (1.00–1.01)	0.0065	-
Serum Albumin (1 g/dL increase)	0.05 (0.02–0.18)	<0.0001	0.21 (0.04–1.02)	0.0526	-
Hypertriglyceridemia (vs. no)	2.24 (1.06–5.48)	0.0334	1.48 (0.57–3.91)	0.4178	-
Low HDL cholesterol (vs. no)	1.65 (0.91–3.06)	0.0981	1.47 (0.57–3.89)	0.4322	-
Antidyslipidemic agents (vs. no)	1.31 (0.72–2.38)	0.3689	-	-	-
Max IMT (1 mm increase)	1.42 (1.07–1.83)	0.0151	1.49 (1.02–2.12)	0.0394	0.0770

Variables with a P-value <0.1 in the univariate model, as well as age, sex, eGFR, and interaction terms of interest (variables with a P-Value for interaction <0.1 in the Table 2 * age ≥ 65 years), were included in the multivariate model. Abbreviations: n, number; CI, confidence interval; P, calculated probability; vs., versus; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; Cre, creatinine; HDL, high-density lipoprotein; Max IMT, maximum measurable intima-media thickness in the entire scanned common carotid arteries, carotid bulbs, and internal carotid arteries.