Kidney Function and Progression of Carotid Intima-Media Thickness in a Community Study

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Background: Limited data exist regarding the relationship between decreased kidney function, carotid intima-media thickness (IMT) progression, and vascular events.

Study Design: A community-based cohort study.

Setting & Participants: 3,364 participants in the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria Study.

Predictor: Quartiles of kidney function level estimated by means of creatinine clearance (Ccr) using the Cockcroft-Gault equation (Ccr <64, 64 to 75, 75 to 89, and >89 mL/min/1.73 m²).

Outcomes & Measurements: Change in carotid IMT during 2 years. Composite clinical study end point is the occurrence of major adverse cardiovascular events, a composite of myocardial infarction, stroke, and vascular death after 2 years.

Results: Baseline mean carotid IMT was 0.79 ± 0.19 (SD) mm. Mean change in carotid IMT was 0.02 ± 0.11 mm/y. Lower Ccr quartile at baseline was associated with a greater change in adjusted mean values: 0.024 (95% confidence interval [CI], 0.020 to 0.027); 0.019 (95% CI, 0.015 to 0.023); 0.012 (95% CI, 0.009 to 0.016); and 0.0077 (95% CI, 0.005 to 0.011), respectively (P < 0.01). After evaluation of change in carotid IMT, 36 patients (1.1%) experienced a fatal and nonfatal vascular event. Subjects with baseline Ccr less than the median (75 mL/min/1.73 m²) and change in carotid IMT greater than the median (0.008 mm/y) had the worst prognosis (log-rank test, P = 0.04). By means of multivariable analysis with the Cox proportional hazard model, lower baseline Ccr (hazard ratio, 1.04; 95% CI, 1.02 to 1.23; P = 0.03 per 1-mL/min/1.73 m² decrease) and faster change in carotid IMT (hazard ratio, 1.15; 95% CI, 1.11 to 1.93; P = 0.01 per 0.1-mm increase) were associated with fatal and nonfatal vascular events.

Limitations: Microalbuminuria, associated with carotid atherosclerosis, was not available.

Conclusion: Decreased kidney function is associated strongly with faster change in carotid IMT. In addition, decreased kidney function and faster change in carotid IMT are associated with cardiovascular events.

INDEX WORDS: Chronic kidney disease; intima-media thickness; cardiovascular mortality.

Epidemiological studies showed that chronic kidney disease (CKD) is a worldwide public health problem.1 Progression toward end-stage renal disease exposes patients to increased risk of the development of vascular disease and cardiovascular morbidity and mortality.2 As a consequence, in subjects with CKD, death is a more likely outcome than progression to end-stage renal disease.3 Although numerous studies4-6 showed an association between decreased kidney function and cardiovascular disease and mortality independent of traditional and nontraditional risk factors, the mechanisms underlying this association are incompletely understood.

Carotid intima-media thickness (IMT) is a useful and noninvasive evaluation of early carotid atherosclerosis, increasingly used to predict future clinical cardiovascular end points in observational and interventional studies. Furthermore, carotid IMT was used as an outcome and exposure variable in studies evaluating risk factors for atherosclerosis and predictors of coronary artery disease and stroke, respectively. More importantly, changes in carotid IMT over time as a marker for atherosclerosis progression have served as an intermediary outcome in interventional trials to assess the effects of therapeutic interventions.7-10 Thus, the issue of arterial structure derived from carotid ultrasonography is of

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relevance because if validated in subjects with CKD, it may help risk stratification of this very high-risk population.

Numerous studies based on carotid ultrasonography documented an association between severe arterial damage and end-stage renal disease. Furthermore, common carotid artery diameter and carotid IMT were associated with cardiovascular disease and all-cause mortality in long-term dialysis patients. However, associations among different levels of kidney disease, carotid IMT progression, and cardiovascular outcomes were not fully investigated. We therefore tested this relationship in participants in the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria (INVADE) Study.

METHODS

Subjects

The INVADE Study is a prospective and population-based cohort study of the elderly. All inhabitants of the community of Ebersberg, Germany, born before 1946 and members of the health insurance company Allgemeine Ortskrankenkasse (AOK) were identified in the AOK database and invited to participate (n = 10,325). In the area of Ebersberg, more than 40% of all inhabitants older than 55 years were AOK members. During 2001 to 2003 (baseline phase), 3,905 subjects followed up the invitation, 3,364 of whom were included in the present study. The remaining subjects were excluded because of incomplete laboratory data (n = 365) and missing (n = 95) or not analyzable (n = 81) carotid IMT. The baseline investigation was done by primary care physicians of the community of Ebersberg (n = 65) and included a standardized questionnaire, medical history, evaluation of several risk factors, physical examination, 12-lead electrocardiogram, and overnight fasting venous blood sample for analysis in a central laboratory. Duplex ultrasonographic examination of the carotid arteries was done in all subjects according to a standardized protocol by 8 experienced investigators after training. All data were entered into a central database after plausibility checks for further evaluation. After the initial baseline investigation, the primary care physician assessed participants every 3 months. Complete evaluations were scheduled after 2 years of follow-up. The local institutional review board approved the study. Details of the study design were recently published in detail.

Cardiovascular Disease Status and Risk Factors

Information about current health status, medical history, lifestyle, cognitive status, mood disorders, drug use, and former cardiovascular risk factors was obtained by means of a computerized questionnaire at baseline. Risk factors determined included body mass index (BMI; kilograms per meter squared), smoking status, duration of smoking, alcohol consumption, actual medication, social status, education status, arterial hypertension (treatment with antihypertensive medication or documented blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic measured in a standardized fashion), diabetes mellitus (treatment with antidiabetic drugs or overnight fasting serum glucose levels ≥126 mg/dL [≥7.0 mmol/L]), prevalent ischemic heart disease (documented as previous myocardial infarction [MI] or angina pectoris, bypass surgery, or >50% angiographic stenosis of ≥1 major coronary artery), prevalent peripheral artery disease (according to Transatlantic Intersociety Consensus criteria), and prevalent stroke (neurological deficit that persisted >24 hours, evaluated by a neurologist). MI and stroke were diagnosed according to recent recommendations.

Clinical End Points

When subjects enter the INVADE Study, they are continuously monitored for major vascular events through linkage of the study database with the 3-month-visit files from general practitioners, the AOK database, and the municipality. For reported events, additional information was obtained from hospital records, autopsy records, and death certificates. Two physicians (D.S. or H.G.) independently coded all fatal and nonfatal events. The clinical study end point was the occurrence of major adverse cardiovascular events, a composite of MI, stroke, and vascular death.

Definition of Kidney Function

Because a number of factors, such as age, sex, and weight, can influence serum creatinine concentrations, level of kidney function was calculated as creatinine clearance (Ccr) by using the Cockcroft-Gault equation, which includes measures of age, weight, and sex, and was standardized for body surface area (BSA):

\[
\text{Ccr (mL/min/1.73 m^2)} = \frac{[(140 - \text{age}) \times (\text{weight}) \times (0.85 \text{ if female})]}{[\text{72} \times (\text{serum creatinine})]} \times 1.73 \text{ m}^2/\text{BSA}
\]

where serum creatinine is in milligrams per deciliter, age is in years, weight is in kilograms, and BSA is estimated using the Dubois formula:

\[
\text{BSA(m^2)} = 0.20247 \times (\text{height})^{0.725} \times (\text{weight})^{0.425}
\]

where height is in meters and weight is in kilograms. For the purpose of this analysis, we defined CKD as Ccr less than 60 mL/min/1.73 m^2 (<1.00 mL/s/1.73 m^2).

Laboratory Examinations

Overnight fasting blood samples were drawn from each subject and transferred on ice to a central laboratory that performed all analyses. Serum creatinine was assessed by using a kinetic alkaline picrate (Jaffé) method. We used a high-sensitivity assay for measurement of serum high-sensitivity C-reactive protein (hs-CRP). N High Sensitivity CRP, Dade Behring, Eschborn, Germany) with a lower detection level of 0.175 mg/L and a coefficient of variation.
of 7.6%. Intra-assay precision ranges from 3.1% for an hs-CRP content of 0.5 mg/L and 4.0% for an hs-CRP content of 15 mg/L. Inter-assay precision was 2.5% and 2.6%, respectively. Glycosylated hemoglobin (HbA1c) was measured by using high-pressure liquid chromatography separation of hemoglobin fractions with a reference value of 4.0% to 6.0% and a coefficient of variation of 1.8% on a Hi nAuto A1c HA-8140 device (Kyoto Daichii Kakagu; Arkray KDK, Kyoto, Japan). Total homocysteine were measured by using high-performance liquid chromatography with fluorescence detection.23 Fasting blood samples were collected into EDTA tubes containing 3-deazaaneplanocin A (100 mmol/L).24 In these tubes, homocysteine remained stable for up to 72 hours after sampling. All analyses were performed in duplicate, and the mean value was obtained. Intra-assay and interassay precision were 1.6% to 3.0% and 1.9% to 4.4% after 5 weeks, respectively. In addition to these values, cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, and fasting serum glucose were measured.

Ultrasound Imaging

Eight experienced investigators performed duplex ultrasoundography using a standardized study protocol. The initial duplex sonography and follow-up investigation were performed by the same investigator. Ultrasound data were stored on video or digital audio tapes, transferred to the neurovascular laboratory of the Department of Neurology, and digitalized if necessary. Measurements of mean common carotid artery IMT were done in the neurovascular laboratory as previously described in detail25 by using a computer-supported image analysis system (SigmascanPro 5.0; SPSS, Chicago, IL). To enhance the reproducibility of carotid measures, standardized interrogation angles were used according to recommendations described previously.26 In every subject, follow-up measurements were performed at the same location as the initial measurement. Intraobserver and interobserver agreement were evaluated as follows. Carotid IMT measurements were done in 10 healthy subjects older than 55 years by all 8 duplex investigators before study onset. These measurements were repeated 3 times during 3 weeks. From these data, intraobserver and interobserver agreement were calculated using κ statistics. Intraobserver and interobserver agreement for measurement of carotid IMT were 0.93 and 0.83, respectively.

Progression of early carotid atherosclerosis was defined as the difference between the last and first carotid IMT measurements and normalized as change in carotid IMT per year.

Statistical Analysis

All values are given as mean ± SD, 95% confidence intervals (CIs), or counts and percentages. We used χ² tests, independent t-tests, Mann-Whitney U tests, and Spearman rank correlation for univariate analysis, as appropriate. The study population was divided into quartiles according to levels of kidney function or divided according to CKD status. To analyze the relationship between carotid IMT progression and decrease in kidney function, annual change in Ccr was dichotomized (annual decrease ≥3 mL/min/1.73 m² [≥0.05 mL/s/1.73 m²]). This value for the decrease in Ccr was chosen because the annual rate of decrease with normal aging is believed to be approximately 1 mL/min/1.73 m²/y (0.02 mL/s/1.73 m²/y), based on findings from the Baltimore Longitudinal Study of Aging.26 Hence, an annual decrease of 3 mL/min/1.73 m² or greater (≥0.05 mL/s/1.73 m²) was selected to circumvent nonpathological variations in serum creatinine levels that could suggest the presence of progressive kidney disease.27 Carotid IMT differences at

![Figure 1](https://example.com)  
**Figure 1.** Distribution of creatinine clearance (CrCl) of the entire cohort.
baseline and carotid IMT progression changes between subgroups according to Ccr were tested by using multiple linear regression techniques, and covariate-adjusted mean carotid IMT values (least square means) were reported. Additional analyses were performed using an age-adjusted carotid IMT greater than 1.0 mm. This value was selected on the basis of findings of previous population-based studies, in which this clinically relevant cutoff value was associated with cardiovascular outcomes. Survival curves were estimated by using the Kaplan-Meier product-limit method and compared by means of the log-rank-test. Hazard ratios were estimated by using the Kaplan-Meier product-limit method and with cardiovascular outcomes. Survival curves were estimated by using the Cox proportional hazard regression model. All multivariable analysis was adjusted for the same relevant covariates (age, sex, BMI, smoking, prevalent ischemic heart disease, systolic blood pressure, diastolic blood pressure, statin administration, aspirin use, and cholesterol, LDL-C, HbA1c, hs-CRP, and homocysteine levels). For analyses of carotid IMT progression, baseline carotid IMT additionally was included as a continuous covariate. Calculations were performed using JMP 5.01 software (SPSS Inc, Chicago, IL). P less than 0.05 is considered statistically significant.

### RESULTS

**Baseline Characteristics**

We included 3,364 subjects in the analysis, and 551 (16.4%) had CKD at baseline. Distribution of Ccrs of the entire cohort is shown in Fig 1. Mean Ccr in participants with CKD was 50 ± 9 mL/min/1.73 m² (0.83 ± 0.15 mL/s/1.73 m²). Most participants with CKD had moderate kidney disease: 22 (4%) had a Ccr less than 30 mL/min/1.73 m² (<0.50 mL/min/1.73 m²), 101 (18.3%) had a Ccr of 30 to 45 mL/min/1.73 m² (0.50 to 0.75 mL/s/1.73 m²), and 428 (77.7%) had a Ccr of 45 to 60 mL/min/1.73 m² (0.75 to 1.00 mL/s/1.73 m²). Baseline characteristics for the entire group by Ccr level are listed in Table 1. Lower Ccr were associated with older age, female sex, lower BMI, fewer pack-years of smoking, and greater

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1 (&lt;64 mL/min/1.73 m²)</th>
<th>Quartile 2 (64-75 mL/min/1.73 m²)</th>
<th>Quartile 3 (75-89 mL/min/1.73 m²)</th>
<th>Quartile 4 (&gt;89 mL/min/1.73 m²)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>75 ± 7.6</td>
<td>69 ± 7.0</td>
<td>66 ± 5.7</td>
<td>65 ± 5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>295 (35.1)</td>
<td>347 (49.4)</td>
<td>373 (44.2)</td>
<td>359 (42.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 ± 3.7</td>
<td>27.0 ± 3.8</td>
<td>27.6 ± 3.9</td>
<td>30.1 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>5.3 ± 13.4</td>
<td>7.5 ± 16.4</td>
<td>8.4 ± 17.3</td>
<td>8.4 ± 18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>53 (6.3)</td>
<td>78 (9.3)</td>
<td>92 (10.9)</td>
<td>110 (13.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Former</td>
<td>174 (20.7)</td>
<td>216 (25.8)</td>
<td>207 (24.5)</td>
<td>202 (24.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Never</td>
<td>613 (73.0)</td>
<td>544 (64.9)</td>
<td>544 (64.6)</td>
<td>531 (62.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>174 (20.7)</td>
<td>88 (10.5)</td>
<td>81 (9.6)</td>
<td>66 (7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>46 (5.5)</td>
<td>21 (2.5)</td>
<td>25 (2.9)</td>
<td>12 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>209 (24.9)</td>
<td>134 (16)</td>
<td>127 (15.1)</td>
<td>132 (15.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>578 (68.8)</td>
<td>455 (54.3)</td>
<td>448 (53.1)</td>
<td>441 (52.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>140 ± 19</td>
<td>140 ± 18</td>
<td>139 ± 17</td>
<td>139 ± 18</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 ± 10</td>
<td>82 ± 10</td>
<td>83 ± 9</td>
<td>83 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin administration</td>
<td>144 (17.1)</td>
<td>131 (15.6)</td>
<td>148 (17.6)</td>
<td>116 (13.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>129 ± 38</td>
<td>132 ± 37</td>
<td>132 ± 38</td>
<td>128 ± 42</td>
<td>0.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>140 ± 73</td>
<td>136 ± 80</td>
<td>142 ± 79</td>
<td>157 ± 98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9 ± 0.87</td>
<td>5.8 ± 0.81</td>
<td>5.8 ± 0.81</td>
<td>5.9 ± 0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.1 ± 0.46</td>
<td>0.90 ± 0.15</td>
<td>0.82 ± 0.13</td>
<td>0.70 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline Ccr (mL/min/1.73 m²)</td>
<td>52 ± 9</td>
<td>69 ± 9</td>
<td>82 ± 4</td>
<td>104 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>4.5 ± 6.3</td>
<td>3.4 ± 4.7</td>
<td>3.8 ± 5.7</td>
<td>3.7 ± 5.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Homocysteine (mg/L)</td>
<td>8.5 ± 4.3</td>
<td>7.0 ± 3.6</td>
<td>6.4 ± 3.4</td>
<td>6.3 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Values expressed as mean ± SD or number of participants (percent). To convert LDL-C in mg/dL to mmol/L, multiply by 0.02586; triglycerides in mg/dL to mmol/L, multiply by 0.01129; Ccr in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to µmol/L, multiply by 76.26; homocysteine in mg/L to µmol/L, multiply by 7.397.

Abbreviations: HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; Ccr, creatinine clearance; hs-CRP, high-sensitivity C-reactive protein.
Kidney Function and Carotid Atherosclerosis

Table 2. Association Between Kidney Function at Initiation of Study and Baseline Carotid Intima-Media Thickness

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartile 1 (&lt;64 mL/min/1.73 m²)</th>
<th>Quartile 2 (64-75 mL/min/1.73 m²)</th>
<th>Quartile 3 (75-89 mL/min/1.73 m²)</th>
<th>Quartile 4 (&gt;89 mL/min/1.73 m²)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.84 (0.82-0.86)</td>
<td>0.79 (0.76-0.84)</td>
<td>0.78 (0.75-0.81)</td>
<td>0.76 (0.75-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.82 (0.78-0.85)</td>
<td>0.80 (0.75-0.84)</td>
<td>0.79 (0.75-0.83)</td>
<td>0.77 (0.72-0.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.81 (0.78-0.86)</td>
<td>0.79 (0.75-0.81)</td>
<td>0.79 (0.75-0.83)</td>
<td>0.76 (0.72-0.78)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Note: Carotid intima-media thickness is measured in millimeters. Covariate-adjusted mean carotid intima-media thickness values (least-square means) are shown. All other covariates are set to their mean levels. To convert creatinine clearance in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

*Adjusted for age, sex, body mass index, smoking, prevalent ischemic heart disease, systolic blood pressure, diastolic blood pressure, statin administration, aspirin use, and cholesterol, low-density lipoprotein cholesterol, glycosylated hemoglobin, high-sensitivity C-reactive protein, and homocysteine levels.

The association between impaired kidney function and carotid IMT at baseline is listed in Table 2. In age-adjusted analysis, the least square means (95% CI) of carotid IMT was associated with impaired kidney function (P < 0.01 for trend; Table 2). The direction of the relationship was consistent with increased subclinical atherosclerosis with advanced kidney disease, ie, greater carotid IMT at baseline was significantly associated with level of kidney function impairment at the initiation of the observation period. After adjustments for demographics, BMI, smoking, prevalent ischemic heart disease, systolic blood pressure, diastolic blood pressure, statin administration, aspirin use, and cholesterol, LDL-C, HbA1c, hs-CRP, and homocysteine levels, carotid IMT increased with decreasing Ccr, from 0.76 mm (95% CI, 0.72 to 0.78) in subjects in quartile 4 to 0.81 mm (95% CI, 0.78 to 0.86) in subjects in quartile 1 of kidney function level (P = 0.02 for trend; Table 2). Additional analysis was performed to establish an association between carotid IMT at baseline and subjects with and without CKD at the initiation of the study. In the fully adjusted model, carotid IMT was 0.84 mm (95% CI, 0.82 to 0.86) for participants with CKD and 0.79 mm (95% CI, 0.76 to 0.81) for subjects without kidney disease (P = 0.02).

Association Between Kidney Function and Carotid IMT Progression

Figure 2 shows the distribution of carotid IMT progression in the entire population, and the relationship between level of kidney function impairment at baseline and carotid IMT progression is listed in Table 3. After multivariable adjustment, a significant trend for progression of carotid IMT was noticed for decreasing Ccrs at baseline (P < 0.01 for trend; Table 3). The least square means (95% CI) of carotid IMT progression increased almost 3-fold across kidney function quartiles (Table 3). For example, after multivariable adjustment, participants in quartile 4 had carotid IMT progression of 0.008 mm/y (95% CI, 0.005 to 0.011) compared with subjects in quartile 1 of kidney function who progressed by 0.024 mm/y (95% CI, 0.020 to 0.027). In addition, subjects with CKD at baseline had significant progression of subclinical atherosclerosis (0.022 mm/y; 95% CI, 0.017 to 0.027) compared with subjects without CKD (0.013 mm/y; 95% CI, 0.011 to 0.015; P < 0.01).

Additional analysis was performed on the longitudinal relationship between decrease in kidney function, defined as Ccr of 3 mL/min/1.73 m² or greater (≥0.05 mL/s/1.73 m²/y). In the fully adjusted model (Table 4), participants with a rapid decrease in kidney function had significantly greater carotid IMT progression compared with subjects with a decrease in kidney function less than 3 mL/min/1.73 m²/y (<0.05 mL/s/1.73 m²/y; 0.015 mm/y; 95% CI, 0.011 to 0.019).
versus 0.005 mm/y (95% CI, 0.002 to 0.008; \( P < 0.01 \)).

Additional analysis was performed on the cross-sectional and longitudinal association between baseline kidney function and significant subclinical atherosclerosis, defined as an age-adjusted carotid IMT greater than 1.0 mm. In the entire cohort, 412 subjects had a baseline age-adjusted carotid IMT greater than 1.0 mm. We observed a strong association between this clinical cutoff value and baseline kidney function. Participants with an age-adjusted carotid IMT greater than 1.0 mm at baseline had Ccrs of 72 ± 23 mL/min/1.73 m² (1.20 ± 0.38 mL/s/1.73 m²) compared with Ccrs of 78 ± 20 mL/min/1.73 m² (1.30 ± 0.33 mL/s/1.73 m²) in participants with an age-adjusted baseline carotid IMT less than 1.0 mm (\( P < 0.001 \)). In addition, participants with a baseline age-adjusted carotid IMT greater than 1.0 mm had lower Ccrs at the end of follow-up compared with subjects with a carotid IMT less than 1.0 mm (67 ± 21 versus 71 ± 21 mL/min/1.73 m² [1.12 ± 0.35 versus 1.18 ± 0.35 mL/s/1.73 m²]; \( P < 0.01 \)).

### Relationship Between Baseline Kidney Function, Carotid IMT Progression, and Fatal and Nonfatal Vascular Events

During year 3 of the study period (ie, period after evaluation of carotid IMT progression was completed), 36 patients experienced a fatal or nonfatal vascular event; 23 (0.8%) in the group with a Ccr greater than 60 mL/min/1.73 m² (>1.0 mL/s/1.73 m²) and 13 (2.4%) in the group with a Ccr less than 60 mL/min/1.73 m² (<1.0 mL/s/1.73 m²; \( \chi^2 = 5.4; \) adjusted hazard ratio using Cox regression, 1.8; 95% CI, 1.05 to 7.8; \( P = 0.04 \)). In addition, the interaction carotid IMT progression × Ccr was significant (\( P < 0.01 \)). Therefore, to evaluate the association be-

### Table 3. Association Between Kidney Function at Baseline and Carotid Intima-Media Thickness Progression

<table>
<thead>
<tr>
<th>Model</th>
<th>Quartile 1 (64 mL/min/1.73 m²) (n = 840)</th>
<th>Quartile 2 (64-75 mL/min/1.73 m²) (n = 838)</th>
<th>Quartile 3 (75-89 mL/min/1.73 m²) (n = 843)</th>
<th>Quartile 4 (&gt;89 mL/min/1.73 m²) (n = 843)</th>
<th>( P ) for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.022 (0.016-0.026)</td>
<td>0.016 (0.012-0.019)</td>
<td>0.011 (0.008-0.015)</td>
<td>0.0089 (0.005-0.012)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.030 (0.024-0.035)</td>
<td>0.027 (0.023-0.031)</td>
<td>0.016 (0.012-0.019)</td>
<td>0.008 (0.004-0.013)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>0.024 (0.020-0.027)</td>
<td>0.019 (0.015-0.023)</td>
<td>0.012 (0.009-0.016)</td>
<td>0.0077 (0.005-0.011)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Note: Carotid intima-media thickness measured in millimeters. Covariate-adjusted mean carotid intima-media thickness values (least square means) are shown. All other covariates are set to their mean levels. To convert creatinine clearance in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

*Adjusted for age, sex, body mass index, smoking, prevalent ischemic heart disease, systolic blood pressure, diastolic blood pressure, statin administration, aspirin use, and cholesterol, low-density lipoprotein cholesterol, glycosylated hemoglobin, high-sensitivity C-reactive protein, and homocysteine levels.
between baseline kidney function, carotid IMT progression, and vascular events, the entire cohort was divided into 4 groups on the basis of median baseline Ccr and carotid IMT progression. Kaplan-Meier survival curves showing percentage of subjects with cardiovascular events after 3 years of follow-up as a function of carotid IMT progression during a 2-year period and baseline Ccr (Fig 3) show that the majority of vascular events occurred in subjects with carotid IMT progression greater than the median (0.08 mm/y) plus a Ccr less than the median (75 mL/min/1.73 m² [1.25 mL/s/1.73 m²]), with lower rates of vascular events in participants in the other categories, including a Ccr less than the median, but with carotid IMT progression less than the median (log-rank test, \( P = 0.04 \)). Moreover, in multivariate analysis with the Cox proportional hazard model, each 0.1-mm increase in carotid IMT and 1-mL/min/1.73 m² decrease in Ccr conferred 1.15 (95% CI, 1.11 to 1.93; \( P = 0.01 \)) and 1.04 (95% CI, 1.02 to 1.23; \( P = 0.03 \)) excess hazard for developing a fatal or nonfatal vascular event, respectively.

**DISCUSSION**

The present population-based follow-up study of kidney function and carotid IMT has 2 main findings. First, we found that impairment in kidney function is a strong predictor of greater carotid IMT at baseline and progression of subclinical atherosclerosis independent of traditional risk factors.

**Table 4. Association Between Decrease in Kidney Function and Carotid Intima-Media Thickness Progression**

<table>
<thead>
<tr>
<th>Model</th>
<th>Ccr ≥ 3 mL/min/1.73 m²/y (n = 821)</th>
<th>Ccr &lt; 3 mL/min/1.73 m²/y (n = 2,543)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.020 (0.016-0.024)</td>
<td>0.006 (0.004-0.009)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.017 (0.014-0.02)</td>
<td>0.007 (0.004-0.01)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>0.015 (0.011-0.019)</td>
<td>0.005 (0.002-0.008)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Note: Carotid intima-media thickness measured in millimeters. Covariate-adjusted mean carotid intima-media thickness values (least-square means) are shown. All other covariates are set to their mean levels. To convert Ccr in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviation: Ccr, creatinine clearance.

*Adjusted for age, sex, body mass index, smoking, prevalent ischemic heart disease, systolic blood pressure, diastolic blood pressure, statin administration, aspirin use, and cholesterol, low-density lipoprotein cholesterol, glycosylated hemoglobin, high-sensitivity C-reactive protein, and homocysteine levels and baseline carotid intima-media thickness.
tional and nontraditional cardiovascular risk factors. Second, we showed the dynamic relationship between carotid IMT progression, kidney function, and cardiovascular outcomes, emphasizing the value of the addition of an objective measure of subclinical atherosclerosis (carotid IMT) to Ccr as an estimated measurement of kidney function for better stratification of cardiovascular risk in subjects with decreased kidney function.

Studies of subjects with cardiovascular disease consistently showed that level of kidney function was an independent risk factor for cardiovascular mortality.\(^4\)\(^{,29,30}\) However, there are few published data about the relationship of decreased kidney function as a predictor of carotid IMT progression. In our analysis, the relationship between kidney function and carotid IMT was largely independent of previous cardiovascular complications, as well as traditional and nontraditional cardiovascular risk factors, which might imply that this association underlies a pathogenetic link. Furthermore, our results also confirm previous observations that decreased kidney function is an important risk factor for MI, stroke, and fatal vascular events.\(^4\)

Others investigated the association between kidney function and carotid IMT in patients with moderate to severe decreased kidney function who were not yet on dialysis therapy.\(^31,32\) Our baseline findings are similar to a cross-sectional study\(^31\) of 1,046 Asian subjects. In this study, carotid IMT was significantly greater in subjects with abnormal kidney function, although their cohort was younger and only 7.6% had an estimated glomerular filtration rate less than 60 mL/min/1.73 m\(^2\) (1.00 mL/s/1.73 m\(^2\)). Furthermore, the relationship between baseline kidney function and carotid IMT progression was not evaluated. Our findings are also similar to those from a recent longitudinal study of 203 Asian subjects that found an association between baseline carotid IMT and cardiovascular disease in patients with CKD stages 3 and 4.\(^32\) The absolute value of carotid IMT in subjects with CKD was similar in both cohorts. In contrast to our study, this study did not evaluate the relationship of carotid IMT progression, kidney function, and cardiovascular outcomes. The juxtaposition of these results suggests that subclinical atherosclerosis occurs early in the process of decreased kidney function, and the addition of carotid IMT might improve risk stratification.

Pathophysiological mechanisms for the association between CKD and subclinical atherosclerosis are still unclear, although multiple explanations were proposed.\(^33\) Progression of kidney disease is associated with a number of adverse cardiovascular conditions, including volume expansion secondary to sodium retention, hypertension, and insulin resistance with impaired glucose tolerance.\(^34\) In addition, patients with decreased kidney function have abnormal vascular biological characteristics. Therefore, with progression of kidney disease, a series of abnormalities develop, including increased oxidative stress, worsening inflammation (eg, increased CRP levels), and increased serum homocysteine levels.\(^35\)

The strengths of this study are the large number of patients and complete nature of the data set. Other strengths include the ability to adjust for multiple factors that may affect progression of subclinical atherosclerosis. Despite the comprehensive nature of the data set, this study also has several limitations. First, the definition of kidney disease was based on Ccr rather than more precise measures of kidney function, such as iothalamate clearance. Second, the population consisted of elderly persons, and these findings should be applied with caution to younger patients. Third, the follow-up period for carotid IMT progression of 2 years is relatively short. Finally, we were unable to determine the cause and duration of decreased kidney function and did not have information regarding microalbuminuria or overt proteinuria, which is a well-known predictor of cardiovascular events.\(^36\) It is important to note that we controlled for major traditional and nontraditional cardiovascular risk factors, including hypertension, diabetes, and LDL-C, hs-CRP, and homocysteine levels.

In summary, the present study found that in a general elderly population, impairment in kidney function is associated with adverse changes in arterial structure. Importantly, such changes occur early in the process of kidney function deterioration and are important predictors of cardiovascular outcomes. These results suggest that abnormal kidney function could have some pathogenic role in the progression of atherosclerosis. Additional studies should evaluate whether carotid IMT screening strategies in patients with...
Kidney Function and Carotid Atherosclerosis

kidney dysfunction are effective for risk stratification.

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REFERENCES