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Carotid intima-media thickness progression predicts cardiovascular events in Japanese patients with type 2 diabetes

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Short Running title: IMT progression and CVD

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Abstract

**Aims:** The aim of this retrospective study was to investigate the relationship between progression of carotid intima-media thickness (cIMT) and cardiovascular events in Japanese patients with type 2 diabetes mellitus (T2DM) with free of history of cardiovascular events.

**Methods:** Patients with T2DM (n=342) without history of cardiovascular events whose cIMT was assessed more than twice by ultrasonography were recruited and followed-up for cardiovascular events.

**Results:** During a mean follow-up of 7.6 years, 56 (16.4%) cardiovascular events (27 coronary events and 29 cerebrovascular events) were recorded. Multivariate analysis with the Cox proportional hazard model identified cIMT progression as a significant determinant of cardiovascular events, with a hazard ratio (HR) of 2.24 (95% confidence interval; CI, 1.25-4.03, \( P<0.01 \)), in addition to baseline cIMT. The Kaplan-Meier curves also showed significantly higher event rate in patients with high cIMT progression compared to those with low cIMT progression (log-rank \( \chi^2 = 6.65 \); \( P<0.01 \)). Furthermore, the combination of high baseline cIMT and high cIMT progression was a significant predictor of cardiovascular events.

**Conclusion:** Our findings suggest that cIMT progression, in addition to baseline cIMT, is a predictor of cardiovascular events in patients with T2DM without history of cardiovascular events, and that the combination of cIMT progression and baseline cIMT has a strong predictive power for such events.
Key words: intima-media thickness, cardiovascular and cerebrovascular events, diabetes mellitus,
Introduction

Patients with type 2 diabetes mellitus (T2DM) are at high risk for developing cardiovascular diseases (CVD), which are also one of the main causes of death in these patients [1-4]. Given that not all patients with T2DM develop CVD, identifying patients with high probability of developing these diseases is important for efficient early intervention and treatment that could eventually reduce morbidity and mortality.

The carotid intima-media thickness (cIMT) is a well-established non-interventional surrogate marker for the prediction of cardiovascular (CV) events for the general population [5]. Previous studies showed that basal IMT predicted the incidence of CV events also in patients with T2DM [6, 7]. Based on these findings, cIMT changes measured by repeated cIMT assessment are widely used as a surrogate marker for intervention in clinical studies. However, the association between changes in cIMT and the incidence of CV events has not yet been fully addressed. Recently, it was demonstrated that cIMT progression was associated with the incidence of stroke in subjects with free of prevalent CV events [8]. On the other hand, while the European Lacipidine Study on Atherosclerosis (ELSA) showed a positive association between baseline cIMT and the incidence of stroke, it did not show any association between cIMT change and the incidence of stroke [9]. In addition, recent meta-analysis data also suggested that cIMT progression did not correlate with CV events in the general population [10]. Thus, it remains controversial whether changes in cIMT can predict CV events in contrast to baseline cIMT. Furthermore, there is also
uncertainty about the usefulness of cIMT progression as a predictor of CV events in patients with T2DM.

The aim of this study was to investigate whether cIMT change is a predictor for CV events in Japanese patients with T2DM. In addition, this study also investigated whether the combination of baseline cIMT with cIMT progression provides additional information on the prediction of those events.

Materials and Methods

Subjects. A total of 1,538 patients who had their cIMT assessed at the outpatient clinic of Juntendo University Hospital (1,025 men and 513 women) between 2003 and 2005 were recruited in a cohort study as described previously [6] and their follow up period was extended until May 2012. Among the patients, 783 patients fitting the following criteria were selected for previous study[6]: 1) diagnosis of T2DM, 2) 30-75 years of age, 3) negative history of CVD, 4) without renal replacement therapy or liver cirrhosis because the presence of these diseases influence cIMT [11, 12], 5) without malignancy. Among patients in the previous study, we recruited 342 patients who had carotid ultrasonographic examination at least more than twice for the present study. The hospital ethics committee approved the study protocol, and informed consent was obtained from each patient. This trial was registered with UMIN (no. 000010609).

Data acquisition. Body mass index (BMI) and blood pressure (BP) were measured, and blood samples were obtained at baseline. HbA1c (%) was estimated as an NGSP
(National Glycohemoglobin Standardization Program) equivalent value [13]. HbA1c (mmol/mol) (IFCC : International Federation of Clinical Chemistry) was calculated by the following formula: 
\[ \text{HbA1c (mmol/mol)} = 10.93 \times \text{HbA1c (\%)} - 23.52 \text{ (mmol/mol)} \] [14]. The estimated glomerular filtration rate (eGFR) was calculated by the following formula: 
\[ \text{eGFR (ml/min per 1.73 m}^2) = 194 \times \text{Age}^{-0.287} \times \text{serum creatinine}^{-0.1094} \times 0.739 \text{ (times for females)} \] [15]. CV events were extracted from the medical records, and included cardiovascular death, nonfatal myocardial infarction (abnormal cardiac enzymes level with or without new ST-segment elevation > 0.1 mV or apparition of Q wave), unstable angina (confirmed by abnormal electrocardiogram and angiographically coronary stenosis), and new-onset stable angina [16] diagnosed by cardiologists as defined in previous studies [17-19]. Cerebrovascular events included transient ischemic attack (TIA), which was defined as a brief episode of neurologic dysfunction caused focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction [20] and ischemic stroke diagnosed by neurologists (defined as clinical and radiological evidence of stroke without intracranial hemorrhage).

**Measurements of cIMT.** Ultrasonography of the carotid arteries was performed using an echo-tomographic system (EUB-555 used between 2003 and 2009; Hitachi Medico, Tokyo or LOGIQ P6 used from 2010; GE Healthcare, Tokyo) with a linear transducer (mid-frequency range of 7.5-10 MHz). Scanning of the extracranial carotid arteries in the neck was performed in lateral longitudinal projections and in the transverse projection, as reported previously [21-23]. Three measurements of the common IMT
were made for each side; one at the site of greatest thickness and two at other points (1 cm proximal and 1 cm distal to the site) on the lateral projections of the far wall for each patient and including plaque [24]. The average value of the six IMT measurements (3 from the left side and 3 from the right side) was used as the mean common carotid artery IMT for each patient [24]. All scans were conducted by a single physician while all IMT measurements were performed by another physician, and both were blinded to the clinical information. We have previously reported good intraday and interday reproducibility of our examination [21-23]. The annual change in IMT (mm/year) was calculated by using the following equation: annual change of IMT = (second IMT - initial IMT) / observation period [21, 22]. The second measurements cIMT were performed between 2004 and 2011. In 2010, we changed the instrument for measuring cIMT. At introducing the new instrument, we examined correlation of cIMT values measured by the new instrument to that by the old instrument and found that intraclass correlation coefficient of cIMT values of 120 patients with T2DM measured on the same day by a single physician was 0.89, demonstrating high correlation.

**Risk categories and reclassification.** We classified all patients into two groups according to the baseline cIMT values, the low baseline cIMT group (cIMT <1.10 mm) and the high baseline cIMT group (cIMT ≥1.10 mm), because we recently demonstrated that patients with T2DM who had baseline cIMT ≥1.10 mm were significantly at higher risk for CV events [6] and the cIMT of healthy subjects with non-T2DM was rarely above this value [25]. We also classified all patients into two
groups according to the cIMT progression value; the low cIMT progression group (cIMT progression < median) and the high cIMT progression group (cIMT progression ≥ median). According to the classifications of cIMT and cIMT changes, patients were subclassified into four groups; low baseline cIMT-low cIMT progression group (baseline cIMT < 1.1 mm and cIMT progression < median), low baseline cIMT-high cIMT progression group (baseline cIMT < 1.1 mm and cIMT progression ≥ median), high baseline cIMT-low cIMT progression group (baseline cIMT ≥ 1.1 mm and cIMT progression < median), and high baseline cIMT-high cIMT progression group (baseline cIMT ≥ 1.1 mm and cIMT progression ≥ median). We also investigated whether the combination of baseline cIMT and cIMT progression could provide additional information on the prediction of those events.

**Statistical analysis.** Continuous variables were summarized as mean±standard deviation and categorical variables were represented as percentages. Univariate and multivariate Cox proportional hazards models were used to identify risk factors for primary CV events. Classical atherosclerotic risk factors and markers such as age, gender, BMI, diabetic duration, systolic BP, HbA1c, LDL cholesterol, HDL cholesterol, smoking, eGFR, cIMT, and annual changes in cIMT were assessed as independent variables for modeling. The cumulative event rate for primary CV event was estimated from the Kaplan-Meier survival curves adjusted for age and gender and the difference was compared by the log-rank test. All statistical tests were two-sided with 5% significance level. All analyses were performed using the SAS software version 9.2 (SAS Institute, Cary, North Carolina).
Results

The clinical characteristics of the 342 study patients were as follows; the mean age was 59.0±9.2 years, 57.0% were men, BMI was 24.4±4.1 kg/m², systolic BP was 131.8±17.6 mmHg, estimated duration of T2DM was 9.2±7.3 years and HbA1c (NGSP) was 7.7±1.6% (59.3±20.0 mmol/mol). Baseline cIMT and annual change in cIMT were 1.05±0.23 mm and 0.03±0.11 mm/year, respectively. While patients who had carotid ultrasonographic examination at least more than twice were selected for this study from subjects of the previous study (n=783) [6], there were no differences of age, gender, BMI, BP, HbA1c, estimated diabetic duration, LDL cholesterol levels and HDL cholesterol levels, the number of smoker and baseline cIMT between the study subjects of the present study and those of the previous study (data not shown). During the follow-up period (7.6±1.4 years), 56 (16.4%) CV events, including 27 coronary events (2 acute myocardial infarction, 20 unstable angina and 5 new-onset stable angina), 29 cerebrovascular events (8 TIA and 21 stroke) and no death were recorded in this group.

Table 1 summarizes the characteristics of the patients with no CV events (n=286) and those with events (n=56). Among the classical atherosclerotic risk factors, there were no significant differences in BMI, BP, HbA1c, LDL cholesterol levels and HDL cholesterol levels between the patients with and without CV events (univariate Cox proportional hazard model, Table 1). On the other hand, patients who developed CV events were older, higher rate of current smokers, had higher baseline cIMT, higher
presence of baseline plaque(s) and stenosis(es), and lower eGFR compared to those without events. While the period of cIMT measurement was comparable between the two groups (CV events group: 2.86±1.70 years, CV event-free group: 2.97±1.62 years), patients of the CV events group showed higher cIMT progression compared to those of the non-event group. Although the percentages of users of anti-diabetic drugs, lipid-lowering drugs and anti-thrombotic drugs were similar in both groups, the percentage of CV events group on anti-hypertensive drugs tended to be higher compared to patients of the non-event group (P < 0.1, Table 1).

After adjustment for all risk factors, the multivariable Cox proportional hazard model identified age, BMI, smoking, and baseline cIMT as positive correlates, and eGFR as negative correlate with CV events (Table 2). As a categorical variable, the change in cIMT was also significantly associated with CV events, with a hazard-ratio of 2.24 (95% confidence interval; CI, 1.25-4.03, P<0.01), with cIMT change of ≥ 0.01114 mm/year in the high cIMT progression group, compared with <0.01114 mm/year in the low cIMT progression group. In addition, the Kaplan-Meier curves showed significantly higher event rate in the high cIMT progression group compared to the low cIMT progression group (log-rank $\chi^2=6.65; P<0.01$, Figure 1A), with a hazard ratio of 2.10 (95% CI, 1.21-3.66, P<0.01) derived from Cox proportional hazard model adjusted by age and gender. Similarly, the Kaplan-Meier curves showed significant higher events rate in the high baseline cIMT group (≥1.10 mm) compared to the low baseline cIMT group (log rank $\chi^2= 12.51; P<0.001$, Figure 1B), with a hazard ratio of 2.37 (95% CI, 1.38-4.06, P<0.01) derived from Cox proportional hazard model adjusted by age and gender.
Next, we investigated whether the combination of baseline cIMT and cIMT progression is more useful for prediction of CV events. After dividing the patients into the four groups based on baseline cIMT and cIMT progression, the cumulative events rates for primary CV event were estimated from the Kaplan-Meier survival curves adjusted for age and gender (Figure 2). The CV events rate was the highest in the high baseline cIMT-high cIMT progression group, and the CV event rates were significantly different among the four groups (log rank $\chi^2=24.78; P<0.001$). In fact, the risk for CV event rate was significantly higher in patients of the high baseline cIMT-high cIMT progression group and those of the high baseline cIMT-low cIMT progression group, compared with those of the low baseline cIMT-low cIMT progression group (hazard ratio 5.89, 95% CI, 2.46-14.09, P<0.001, hazard ratio 2.63, 95% CI, 1.03-6.72, P<0.05, respectively), derived from Cox proportional hazard model adjusted by age and gender.

**Discussion**

In the present study, we demonstrated that in addition to other atherosclerotic risk factors such as age, smoking, eGFR and baseline cIMT, cIMT progression correlated significantly with CV events. Furthermore, the results demonstrated for the first time the usefulness of the combination of baseline cIMT and cIMT progression for the prediction of CV events in patients with T2DM.

Theoretically, the annual change of IMT reflects the progression of atherosclerosis, and thus should be a good marker of CV events. However, a recent
meta-analysis demonstrated that the change in cIMT was not associated with CV events in the general population [10]. On the other hand, another group showed the association of cIMT progression with stroke in general population that had some risk factors for CVD [26]. Also, the present study found a significant association between cIMT progression and CV events in patients with T2DM. Generally, measurement of cIMT progression is more difficult than single measurement because random measurement errors at baseline and follow-up are accumulated. Therefore, if cIMT progression was a very small, it could be below the quantities to be detected. In this regard, the cIMT progression rate (0.03 mm/year) observed in the present study is consistent with the previously reported data on Japanese patients with T2DM. (0.034 mm/year) and is more than four times higher than that reported in healthy Japanese population (0.008 mm/year) [27]. Higher annual changes of cIMT in the patients with T2DM may allow a more accurate assessment of progression of atherosclerosis and, thus, increases the sensitivity of cIMT progression for the prediction of CV events in T2DM.

Although patients with T2DM are at a higher risk for CV events compared to non-diabetic patients [1-4], the incidence of myocardial infarction in Japanese patients with T2DM was relatively low, because of the low incidence of myocardial infarction in Japanese (per 1,000 person-years for the Japanese general population: 0.5-2.0) [28-30]. Indeed, the General Practice Research Database study conducted recently in the UK reported the incidence of CV events of 18.3 per 1,000 person-years, and incidence of cerebrovascular events of 11.9 per 1,000 person-years in patients with T2DM [31, 32]. On the other hand, those of Japanese patients with T2DM in the
Hisayama study [2], Japan Diabetic Complication Study (JDCS) [4] and Japan Diabetes Clinical Data Management (JDDM) study [33] were 5.0, 8.3 and 4.4 per 1,000 person-years for coronary heart disease, and 6.5, 7.6 and 3.1 person-years for stroke, respectively.

In this study, the incidence of CV events was 10.72 per 1,000 person-years and that of cerebral vascular events was 11.47 per 1,000 person-years. Both rates were moderately higher than those reported previously in other studies, although the incidence of CV events was markedly lower than in patients of Western countries. In this study, we recruited patients followed at the outpatient clinic of a tertiary hospital, thus it is possible that patients of this study could have more advanced complications than patients followed at a general hospital or general practitioners. The higher CV events rate may also contribute to the positive relationship between cIMT progression and CV events because a small number of CV events often attributes to a lack of statistical power.

A recent meta-analysis study did not report any association between cIMT and CV events in the general population [10]. Based on the fact that there are no established standard methods to measure cIMT, meta-analysis of studies using different imaging modalities conducted in different institutes may reduce the sensitivity of cIMT progression to predict CV events. On the other hand, in this study, we used an unified technique. This could also contribute to the high sensitivity of cIMT progression as a marker of CV events.

Baseline cIMT had been used as a marker of subclinical atherosclerosis and established as a surrogate marker for CV events [5, 7]. In multivariate Cox model after
adjusting for classic risk factors, we also found a high odds ratio for CV events per 0.01 mm increase in baseline cIMT. This finding is consistent with previous studies conducted in the general population [5, 34] and in patients with T2DM [19]. Additionally, the Kaplan-Meier curve showed a significant higher event rate in the high baseline cIMT group (≥1.10 mm) compared to the low baseline cIMT group, similar to our original cohort data [6]. Accordingly, the results confirm that baseline cIMT is an independent predictor of CVD.

Recently, we showed that the combination of Framingham risk score (FRS) [35] and high baseline cIMT has a greater predictive power for CV events compared with FRS alone in patients with T2DM without history of CV events [6]. In this study, we found that the combination of baseline cIMT and cIMT progression has a superior predictive power of CV events. Thus, the combination of these two parameters could be potentially useful marker in clinical setting to identify a subgroup of patients with T2DM at high risk of CV events.

Our study has certain limitations. First, the study was a retrospective sub-analysis of a relatively small sample size, which may cause a selection bias. However, a selection bias may be minimized because there were no significant difference in patient characteristics at baseline between the original populations and this 342 study patients. Second, we evaluated only common cIMT including plaque, and thus the use of different methods to measure IMT or different parameters may yield different results. Third, the period of IMT measurement was not defined. Fourth, only risk factor levels and uses of drugs at baseline measurement were used for all analysis although the different time of measurement may also contribute to the
progression of atherosclerosis. Fifth, we only recruited Japanese patients with T2DM. The obtained data may not be applicable to patients of different ethnicity. Further large-scale prospective studies are required to address these points.

In conclusion, the present study suggests that both cIMT progression and baseline cIMT are useful surrogate markers for CV events in asymptomatic Japanese patients with T2DM, and that their combination has a strong predictive power for CV events. The results highlight the importance of repeated cIMT measurements in clinical setting.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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References


Figure Legends

**Figure 1.** (A) CV events rate curves for the high and low cIMT change progression groups, from Kaplan-Meier method adjusted for age (59 years) and gender (female = 43 %). (B) CV events rate curves for the high and low baseline cIMT groups, from Kaplan-Meier method adjusted for age (59 years) and gender (female = 43 %).

**Figure 2.** CV events rate curves according to the combination of baseline cIMT and cIMT progression from Kaplan-Meier method adjusted for age (59 years) and gender (female = 43 %).
Table 1. Clinical characteristics of study participants.

<table>
<thead>
<tr>
<th></th>
<th>No cardiovascular events (n=286)</th>
<th>Cardiovascular events (n=56)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.2±9.1</td>
<td>62.6±8.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender (men) (%)</td>
<td>58.7</td>
<td>51.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±4.2</td>
<td>25.0±4.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Estimated diabetic duration (years)</td>
<td>9.16±7.33</td>
<td>9.66±7.40</td>
<td>0.79</td>
</tr>
<tr>
<td>Current smoker (yes) (%)</td>
<td>26.9</td>
<td>44.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of anti-diabetic drugs (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulfonyureas (%)</td>
<td>39.5</td>
<td>30.4</td>
<td>0.24</td>
</tr>
<tr>
<td>glinide (%)</td>
<td>9.4</td>
<td>3.6</td>
<td>0.18</td>
</tr>
<tr>
<td>metformin (%)</td>
<td>22.0</td>
<td>21.4</td>
<td>0.96</td>
</tr>
<tr>
<td>glitazone (%)</td>
<td>8.7</td>
<td>7.1</td>
<td>0.68</td>
</tr>
<tr>
<td>α-glucosidase inhibitor (%)</td>
<td>29.4</td>
<td>28.6</td>
<td>0.88</td>
</tr>
<tr>
<td>insulin (%)</td>
<td>17.5</td>
<td>23.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Use of anti-hypertensive drugs (%)</td>
<td>30.8</td>
<td>42.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs (%)</td>
<td>23.1</td>
<td>32.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Use of anti-thrombotic drug (%)</td>
<td>15.4</td>
<td>12.5</td>
<td>0.58</td>
</tr>
<tr>
<td>Systolic blood pressure (mm/Hg)</td>
<td>131.2±17.8</td>
<td>135.0±16.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm/Hg)</td>
<td>78.3±10.1</td>
<td>79.5±10.0</td>
<td>0.46</td>
</tr>
<tr>
<td>HbA1c (NGSP) (%)</td>
<td>7.69±1.65</td>
<td>7.73±1.26</td>
<td>0.59</td>
</tr>
<tr>
<td>HbA1c (IFCC) (mmol/mol)</td>
<td>59.0±21.0</td>
<td>60.9±13.8</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.13±0.73</td>
<td>3.28±0.69</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.41±0.41</td>
<td>1.33±0.35</td>
<td>0.14</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>86.4±23.0</td>
<td>75.3±20.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline cIMT (mm)</td>
<td>1.03±0.21</td>
<td>1.17±0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cIMT progression (mm/year)</td>
<td>0.01 (-0.01, 0.04)</td>
<td>0.03 (-0.01, 0.07)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are mean±SD or median (range: 25% to 75%) or percentage of patients. P values were calculated from unadjusted Cox proportional hazard models for time to CV event.

cIMT, carotid intima media thickness; eGFR, estimated glomerular filtration rate; IFCC, International Federation of Clinical Chemistry
Table 2. Results of multivariate Cox proportional hazard models for the incidence of CV events.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.04</td>
<td>(1.01-1.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.71</td>
<td>(0.92-3.16)</td>
<td>0.09</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.11</td>
<td>(1.02-1.20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Estimated diabetic duration (years)</td>
<td>0.99</td>
<td>(0.95-1.03)</td>
<td>0.57</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>1.00</td>
<td>(0.98-1.01)</td>
<td>0.61</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.04</td>
<td>(0.87-1.23)</td>
<td>0.70</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>1.20</td>
<td>(0.78-1.88)</td>
<td>0.40</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.53</td>
<td>(0.23-1.24)</td>
<td>0.14</td>
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<tr>
<td>eGFR(mL/min/1.73 m²)</td>
<td>0.98</td>
<td>(0.97-0.99)</td>
<td>0.03</td>
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<td>Smoking (yes)</td>
<td>2.21</td>
<td>(1.27-1.20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline cIMT (0.01 mm)</td>
<td>1.02</td>
<td>(1.01-1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cIMT change (≥median)</td>
<td>2.24</td>
<td>(1.25-4.03)</td>
<td>&lt;0.01</td>
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</table>

The multivariate Cox proportional hazards model was applied to the incidence of CV events.

The median value of cIMT change was 0.01114 mm/year.

cIMT, carotid intima-media thickness; eGFR, glomerular filtration rate;