Carotid artery intima-media thickness and plaque score can predict the SYNTAX score

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Aims
There are few reports demonstrating a relationship between carotid artery ultrasound (carotid-US) findings and the complexity of coronary artery disease. We aimed to examine the relationship between carotid-US findings and the severity of the SYNTAX score (SXscore).

Methods and results
Subjects were 501 consecutive patients who underwent carotid-US and first coronary angiography from December 2008 to January 2011. Carotid-US was used to determine the mean common carotid artery intima-media thickness (meanIMT) and the plaque score (PS). The prevalences of low (0–22), intermediate (23–32), and high (≥33) SXscore patients were 84.8, 7.4, and 7.8%, respectively. The SXscore was correlated with the meanIMT (Spearman’s rank correlation coefficient; \( r = 0.442, P < 0.0001 \)) and the PS (\( r = 0.544; P < 0.0001 \)). The odds ratios associated with the meanIMT and the PS for prediction of an intermediate or the high SXscore were 1.24 and 1.31, respectively. The areas under the receiver-operating characteristic curves for the meanIMT and the PS to predict the intermediate or the high SXscore were 0.791 and 0.846, respectively. When we set the cut-off value of a meanIMT of 0.9 mm, the sensitivity was 92.1% for intermediate or the high SXscore. Similarly, a cut-off level of a PS of 5 presented a sensitivity of 96.1%. A meanIMT \( \geq 0.9 \) mm and a PS \( \geq 5 \) had negative predictive values of 97.3 and 98.6%, respectively, for intermediate or high SXscore.

Conclusion
Carotid-US parameters have predictive value for the SXscore. In addition, the PS and the meanIMT showed excellent negative predictive value for the presence of complex coronary artery lesions.

Keywords
SYNTAX score • Carotid artery ultrasound • Intima-media thickness • Plaque score

Introduction
Guidelines for triaging patients for cardiac catheterization recommend risk assessment and non-invasive testing.\(^1\)\(^–\)\(^3\) However, the effectiveness of non-invasive tests is still insufficient. Even if tests, including ECG, exercise or pharmacologic stress tests, radionuclide, echo, CT scans, or other heart scans, are performed before coronary angiography, the diagnostic yield of elective cardiac catheterization was <40%.\(^4\)

There are numerous reports on the relationship between carotid artery ultrasound (carotid-US) findings and the prevalence of coronary artery disease. Most epidemiologic and clinical studies are based on a measurement of the intima-media thickness (IMT). Previous studies have shown associations between the IMT and coronary artery disease.\(^5\)\(^–\)\(^9\) In contrast, some studies have shown that the existence of carotid plaques is more strongly associated with cardiovascular risk than is a diffuse increase in the IMT.\(^10\) For the quantification of such plaques, the plaque score (PS) has been used, and it has been shown that the PS is associated with stroke risk and the presence of coronary artery disease.\(^11\)\(^–\)\(^13\) However, there have only been a few previous studies that have assessed the association between the complexity of coronary artery disease and the carotid-US findings. The SYNTAX trial demonstrated that the SYNTAX score (SXscore), which represents lesion complexity, correlated with the prognosis among patients who underwent coronary revascularization.\(^14\) We aimed to examine the relationship between carotid-US findings and the severity of the SXscore.

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Methods

Study patients
We considered 501 consecutive patients admitted to Toho University Ohashi Medical Center from December 2008 to January 2011 who underwent carotid-US and first coronary angiography. Coronary angiography was performed to evaluate ischaemic heart disease or cardiomyopathy and as the preoperative investigation for ischaemic heart, aortic disease, or valvular disease. Our study complied with the Declaration of Helsinki, and written informed consent was obtained from all patients.

Assessment of carotid ultrasonography
The severity of carotid artery atherosclerosis was estimated using the mean common carotid artery (CCA) intima-media thickness (meanIMT) and PS. Carotid-US was used to evaluate the meanIMT and the PS. High-resolution B mode, colour Doppler and pulse Doppler ultrasonography of both carotid arteries were performed with an ultrasound scanner (Aplio XV, Apio XG, Xario, Toshiba, Inc., Tokyo, Japan) equipped with a 7.5-MHz linear array transducer by a same experienced sonographer. The sonographer and the interpreting cardiologist were blinded to the angiographic findings. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The high-resolution images of the far wall of the bilateral CCA, internal carotid arteries (ICA), and carotid bulbs were according to recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo (Figure 1). At least three measurements were taken over a 1-cm length of far wall of each CCA segment, and these measurements on both sides were averaged to obtain the meanIMT. When plaque was present in the segment used for measuring the meanIMT, the plaque thickness was averaged into the meanIMT measurement.

Plaque was designated as focal intima-media thickening ≥1.1 mm. The PS was computed by adding the maximal thickness in millimetres of plaques in each segment on both sides (A + B + C + thickness of the contralateral carotid artery plaques) (Figure 2). Segment 1 (S1) was the region of the ICA that was <15 mm distal to its bifurcation from the CCA. Segment 2 (S2) was the region of the ICA and the CCA that was <15 mm proximal to the bifurcation. Segment 3 (S3) was the region of the CCA that was >15 mm and <30 mm proximal to the bifurcation. Segment 4 (S4) was the region of the CCA that was >30 mm proximal to the bifurcation and below the flow divider. The length of individual plaques was not considered in determining the PS (Figure 2).

The SYNTAX score and angiographic analysis
Based on the baseline diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm was scored separately, and these scores were added together to provide the overall SXscore, which was calculated using the SXscore algorithm. This algorithm is available on the SYNTAX website. The SXscore of patients was independently assessed by two experienced interventional cardiologists who were blinded to the carotid-US data. They had experience with calculating the SXscore of >100 patients before assisting in our study. The κ value for inter-observer variability that was used to estimate the SXscore was 0.75, whereas the κ value for the intra-observer variability was 0.86. In cases of disagreement regarding the SXscore, the average of the values from the two readers was used as the final value.

Statistical analysis
We used the Kolmogorov–Smirnov test to evaluate normal distribution. Continuous variables are presented as means ± SDs or medians and the inter-quartile range. Categorical variables are presented as counts or proportions (percentages). To predict the presence of coronary artery disease or intermediate or high SXscore, logistic regression analysis (forced entry methods) was used. First, we analysed an association between the SXscore status and sex, all coronary risk factors and carotid ultrasound findings. Only those factors presented P < 0.05 in univariate analysis were moved forwards to the final model. Correlations between variables were analysed by Spearman’s correlation coefficient by rank. Receiver–operator characteristic (ROC) curves were constructed to assess the best meanIMT and PS values optimizing sensitivity for the identification of the presence of coronary artery disease or intermediate or high-SXscore patients. To reduce the false-negative rate, the sensitivity was given priority over the specificity. The area under the ROC curve and 95% confidence limits were used to assess the predictive power for coronary artery disease. A P-value < 0.05 was considered significant. SPSS ver.17 (SPSS Japan, Inc., Tokyo) was used for the analyses.
Results

Patient characteristics

Patient characteristics are shown in Table 1. The median of the age was 70 years old; 315 (62.9%) were male, and 88 (17.6%) had diabetes mellitus. The low- (0–22), intermediate- (23–32), and high- (33 and over) SXscore patients numbered 425 (84.8%), 37 (7.4%), and 39 (7.8%), respectively. The SXscore of 283 patients (56.5%) was 0. The median values of the meanIMT and the PS were 0.9 and 5.6, respectively.

Correlation between the SYNTAX score and carotid artery ultrasound findings

The SXscore was correlated with the meanIMT (Spearman’s rank correlation coefficient; $r = 0.442; P < 0.0001$) and the PS ($r = 0.544; P < 0.0001$) (Figure 3). When the population was limited to the patients with coronary artery disease, the SXscore was correlated with the meanIMT ($r = 0.385; P < 0.0001$) and the PS ($r = 0.482; P < 0.0001$) (see Supplementary material online, Figure S1).

Prediction of the presence of coronary artery disease or complex lesion

The odds ratios associated with the meanIMT (each 0.1 mm) and the PS (each 1) for prediction of the presence of coronary artery disease were 1.23 (95% CI: 1.16–1.30; $P < 0.001$) and 1.23 (95% CI: 1.17–1.29; $P < 0.001$), respectively. After adjustments for all cardiovascular risk factors, sex, and age, only the PS remained independently associated with the presence of coronary artery disease (odds ratio: 1.22; 95% CI: 1.14–1.31; $P < 0.001$) (Table 2). The odds ratios associated with the meanIMT (each 0.1 mm) and the PS (each 1) for the prediction of intermediate or high SXscore were 1.24 (95% CI: 1.17–1.32; $P < 0.001$) and 1.31 (95% CI: 1.23–1.39; $P < 0.001$), respectively. After adjustments for all cardiovascular risk factors, sex, and age, only the PS remained independently associated with an intermediate or high SXscore (odds ratio: 1.31; 95% CI: 1.20–1.43; $P < 0.001$) (Table 3). The areas under the ROC curves for the meanIMT and the PS to predict the presence of coronary artery disease were 0.688 (95% CI: 0.640–0.736; $P < 0.0001$) and 0.756 (95% CI: 0.713–0.798; $P < 0.0001$), respectively (Figure 4). The areas under the ROC curves for the meanIMT and the PS to predict intermediate or high SXscore were 0.791 (95% CI: 0.738–0.844; $P < 0.0001$) and 0.846 (95% CI: 0.802–0.890; $P < 0.0001$), respectively (Figure 5).

Table 1 Patients characteristics

<table>
<thead>
<tr>
<th>Subject</th>
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<tbody>
<tr>
<td>Total number</td>
<td>501</td>
</tr>
<tr>
<td>Male (%)</td>
<td>315 (62.9)</td>
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<tr>
<td>Age</td>
<td>70.0 (62, 78)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>88 (17.6)</td>
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<tr>
<td>Hypertension (%)</td>
<td>282 (56.3)</td>
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<tr>
<td>Hyperlipidaemia (%)</td>
<td>180 (35.9)</td>
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<td>Current smoking</td>
<td>110 (22.0)</td>
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<tr>
<td>Haemoglobin A1c (%)</td>
<td>5.30 (5.00, 5.80)</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>102 (91, 116)</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>182 ± 37</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mg/dL)</td>
<td>103 (81, 126)</td>
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<tr>
<td>High density lipoprotein cholesterol (mg/dL)</td>
<td>53.3 ± 15.1</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>108 (76, 145)</td>
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<tr>
<td>Mean-CCA-IMT</td>
<td>0.90 (0.75, 1.15)</td>
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<td>Plaque score</td>
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<tr>
<th>Coronary angiography for</th>
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<tr>
<td>Ischaemic heart disease (%)</td>
<td>3</td>
</tr>
<tr>
<td>Cardiomyopathy (%)</td>
<td>174 (34.7)</td>
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<tr>
<td>Valvular disease (%)</td>
<td>4 (0.8)</td>
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<tr>
<td>Cardiac tumour (%)</td>
<td>50 (10.0)</td>
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<td>Aortic disease (%)</td>
<td>220 (43.9)</td>
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<table>
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<tr>
<th>SYNTAX score</th>
<th>425 (84.8)</th>
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<tr>
<td>Low (0–22) (%)</td>
<td>37 (7.4)</td>
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<tr>
<td>Intermediate (23–32) (%)</td>
<td>39 (7.8)</td>
</tr>
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</table>

mean ± SD, median (25th; 75th percentiles).

Figure 3 (A) Correlation between the SYNTAX score and the mean common carotid artery intima-media thickness. (B) Correlation between the SYNTAX score and the plaque score.
Diagnostic accuracy of carotid artery ultrasound

When we set the cut-off value to predict the presence of coronary artery disease to a meanIMT of 0.9 mm, the sensitivity was 70.9% and false-positive rate was 43.1%. Similarly, the cut-off value for the PS of 5 presented a sensitivity of 75.5% and false-positive rate of 41.3%. A meanIMT $\geq 0.9$ mm (55.3% of patients) and a PS $\geq 5$
(56.3% of patients) had negative predictive values of 71.4 and 75.3%, respectively, for the presence of coronary artery disease (see Supplementary material online, Figure S2). In contrast, when we set the cut-off value to predict intermediate or high SXscore to a meanIMT of 0.9 mm, the sensitivity was 92.1%, and the false-positive rate was 48.7%. Similarly, a cut-off value for the PS of 5 presented a sensitivity of 96.1% and a false-positive rate of 49.2%. A meanIMT ≥0.9 mm and a PS ≥5 had negative predictive values of 97.3 and 98.6%, respectively, for the intermediate or high SXscore (see Supplementary material online, Figure S3). Figure 6 demonstrates representative cases of true positive and true negative carotid-US findings with corresponding angiographic findings.

**Discussion**

The principal finding of our study is that carotid-US findings correlate with the complexity of coronary artery disease. Many previous studies have demonstrated the relationship between carotid-US
findings and the prevalence or severity of coronary artery disease. However, the evaluation of disease severity was limited to the number of stenosed coronary vessels. The relationship between carotid-US and the complexity of coronary artery disease has not been investigated. From the aspect of lesion complexity, a recent paper has shown that the SXscore is used to assess the optimal revascularization strategy between percutaneous coronary intervention (PCI) and coronary artery bypass grafting for patients with left main and/or three-vessel coronary disease. In the present study, we showed that carotid-US findings can predict the presence of complex coronary artery disease and are correlated with the degree of complexity. Previous studies have shown that the ability of the PS to identify the presence or severity of coronary artery stenosis is equal to or better than that of the IMT. However, coronary artery disease complexity was not assessed in these reports. In our study, logistic regression analysis was performed to identify significant predictors of the presence of complex coronary artery disease, and the PS showed higher predictive value than the meanIMT. In addition, the PS presented independent predictive value for the presence of coronary artery disease and complex coronary artery disease, but the meanIMT did not. A wider range observation of the carotid arteries than that for the meanIMT is required to obtain PS. Therefore, the PS value may represent the atherosclerotic condition of the carotid artery more precisely than the meanIMT value. This may explain the superiority of the PS in predicting the status of coronary artery disease.

From the ROC curve, we set cut-off values of a meanIMT of 0.9 mm and a PS of 5 to predict the presence of coronary artery disease and the intermediate or the high SXscore. These values seem to be too close to normal values, >40% of patients were classified to normal criteria, and a high false-positive rate was observed. However, these cut-off values showed excellent sensitivity and negative predictive value. When we use carotid-US to triage candidates for invasive coronary angiography, high sensitivity (a low false-negative rate) is the most important factor. We believe that the cut-off value used in our study is acceptable.

A previous report showed that the SXscore independently predicted major adverse cardiovascular and cerebrovascular event (MACCE) outcomes in patients who underwent PCI using sirolimus-eluting stents. Therefore, the SXscore is a useful tool to risk-stratify outcome in patients with extensive coronary artery disease undergoing PCI. It is also meaningful to predict the patients with an intermediate or high SXscore through the use of carotid-US. Many previous papers have showed that carotid-US findings can predict life prognosis or the risk of cardiovascular events. Therefore, investigation of the correlation between carotid-US findings and the SXscore is meaningful.

This study has some limitations. First, the completely occluded part of the carotid artery cannot be summed in the PS. Therefore, the PS values of patients with completely occluded carotid arteries do not accurately reflect the severity of the carotid lesions because these scores are too low. This might affect the final results. Second, because the patients enrolled in our study were suspected to have ischaemic heart disease, these subjects have a relatively higher risk than the healthy population. Therefore, it is not clear whether our results will aid in screening the general asymptomatic population (for example, at a health check-up). In addition, the finding that age is not an independent predictor (Tables 2 and 3) may have been affected by this selection bias. Third, the patients showed relatively low SXscores, and over 50% of patients presented an SXscore of 0. Fourth, the carotid-US findings were obtained by a same experienced sonographer. The intra-observer coefficient of the variation (CV) was 3.1% and that of the PS was 3.4%. The inter-observer CV with a different experienced sonographer of the meanIMT was 4.2% and that of the PS was 4.5%. The inter- and intra-observer variabilities were calculated retrospectively.

**Clinical implication**

Non-invasive testing provides information on lesion complexity that is important for decision making by cardiologists. The suspicion of the prevalence of complex coronary lesions encourages active investigation for generalized atherosclerotic disease.

**Conclusion**

Carotid-US parameters have predictive value for the SXscore. In addition, the PS and the meanIMT showed excellent negative predictive value for the presence of complex coronary artery lesions. Large prospective studies are further required to establish the link between these parameters and the complexity of coronary artery disease.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Conflict of interest:** none declared.

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Carotid artery intima-media thickness and plaque score


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