Different Impacts of Cardiovascular Risk Factors on Arterial Stiffness versus Arterial Wall Thickness in Japanese Patients with Type 2 Diabetes Mellitus

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Aim: We statistically investigated whether the impact of cardiovascular risk factors on arterial stiffness would be different from that on arterial wall thickness.

Methods: We analyzed 1648 Japanese type 2 diabetic patients. Arterial stiffness was evaluated by pulse wave velocity (PWV) and wall thickness was assessed with carotid intima-media thickness (IMT) by ultrasonography. We developed a common regression model to PWV and IMT by extending the linear mixed model and statistically detected the difference in the impact of cardiovascular risk factors between the two indices.

Results: There was a significant correlation between PWV and IMT ($r=0.365$, $p<0.001$). Sex, diabetic duration, hemoglobin A1c levels, and the presence of retinopathy and cardiovascular disease were comparable independent risk factors for elevated PWV and IMT. On the other hand, the impact of age, systolic blood pressure, and low- and high-density lipoprotein cholesterol levels were significantly different between the two measurements (all $p<0.05$). Cholesterol levels were significantly associated with IMT but not with PWV. Age and systolic blood pressure had a significant impact on both measurements, but the impact on PWV was significantly greater than that on IMT. Indeed, patients with low IMT but with advanced age and high systolic pressure had high PWV, whereas patients with low PWV but with impaired cholesterol levels had high IMT.

Conclusion: The extended linear mixed model statistically confirmed that the impact of cardiovascular risk factors on elevated PWV and IMT were not identical in Japanese patients with type 2 diabetes mellitus.


Key words: Arterial stiffness, Pulse wave velocity, Arterial wall thickness, Intima-media thickness, Linear mixed model

Introduction

Type 2 diabetic patients are at a high risk for acquiring cardiovascular diseases1, 2, partly because they are more susceptible to a prolonged hyperglycemia, which accelerates atherosclerosis3), and partly because they often suffer from other proatherogenic comorbidities, such as hypertension4, 5) and dyslipidemia6, 7). For these reasons, various risk factors are involved in the development of atherosclerosis in type 2 diabetic patients8, 9).

The progression of atherosclerosis can be clinically evaluated by some examinations, which are able to identify different atherosclerotic aspects. The measurement of pulse wave velocity (PWV) is a standard method, which can quantify the severity of arterial
stiffness and show the structural and functional properties of the arterial wall. Another standard technique that is used is carotid ultrasonography, by which the intima-media wall thickness (IMT) of the artery, which shows the structural change of arterial wall, can be evaluated.

Previous studies suggested that the risk factors associated with arterial stiffness and wall thickness were not identical. However, those studies analyzed the impact of risk factors on the two atherosclerotic aspects separately and did not make any direct comparisons. A significant impact of a risk factor on one aspect but not on the other does not necessarily mean that there exists a statistically significant difference in the impact. Furthermore, these conventional analytic approaches undoubtedly overlooked a difference in the impact of a risk factor when the risk factor had a significant impact on both aspects. In the previous studies, it remained unclear whether there was any significant difference in the impact of risk factors between arterial stiffness and wall thickness and which risk factors would more strongly influence arterial stiffness than wall thickness and vice versa.

**Aim**

In the current study, we developed a common regression model to arterial stiffness and wall thickness by extending the linear mixed model and used it to statistically investigate whether the impact of risk factors would be different between the two atherosclerotic aspects in Japanese patients with diabetes mellitus.

**Methods**

**Study Population**

We used a clinical database obtained from the Study of Order-Made multiple Risk Factor Intervention Trial (OMRFIT). The OMRFIT study is an ongoing multi-center cohort study to investigate the genetic risk factors for diabetic complications, which enrolled over 4,000 diabetic study patients. The study was approved by the human ethics committee of Osaka University. A written informed consent was obtained from every participant. The current study included type 2 diabetic patients who had both PWV and IMT measured at either Osaka University Hospital or Naka Memorial Clinic at baseline in 2005. During the period, a total of 1785 participants had PWV and IMT measured at the two institutions. We excluded any patients with peripheral arterial disease (defined as ankle-brachial index of ≤ 0.90 or ≥ 1.40) because the presence of the disease was expected to affect their PWV measurements. We also excluded those with data missing on variables of interest and those whose triglycerides levels exceeded 400 mg/dl levels. The latter were excluded because low-density lipoprotein (LDL) cholesterol levels could not be calculated by the Friedewald's formula. Consequently, the remaining 1648 patients were included in the current analysis.

**Assessment of Arterial Stiffness**

Arterial stiffness was evaluated according to the brachial-ankle PWV (ba-PWV), using an automated apparatus (BP-203RPE II form PWV/ABI; Omron Healthcare Co., Ltd., Kyoto, Japan). The apparatus can measure brachial-ankle PWV automatically; the detailed measurement principle was reported previously. In brief, four oscillometric cuffs, connected to a plethysmographic sensor that determines volume pulse form and to an oscillometric pressure sensor that simultaneously measures blood pressure, were wrapped on the bilateral brachia and ankles, whereas electrocardiogram electrodes were placed on the wrists. They were simultaneously pressurized to the approximate value of the patient's diastolic pressure so that the pulse volume waveforms were recorded using semiconductor pressure sensors. The PWV was automatically calculated from the path length from the suprasternal notch to the brachium and ankle, which was estimated from height by the prespecified algorithm, and the time interval between the wave front of the brachial waveform and that of the ankle waveform. Two readings of PWV were measured at the same time on the right side and left side, respectively, and the higher PMV of these readings was used as the representative value for each individual.

**Assessment of Arterial Wall Thickness**

Arterial wall thickness was evaluated with the maximum value of IMT (max-IMT) that was measured by carotid ultrasonography; B-mode ultrasonography of the carotid artery was performed using an ultrasound machine (SDU2200, Shimazu Medical Inc., Japan) with a 7.5-MHz linear transducer. In accordance to the guidelines of the Japan Society of Ultrasonics, all scanning was conducted by experienced laboratory physicians using the same ultrasound system and the same measuring method. Scanning of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (i.e., anterior-oblique, lateral, and posterior-oblique). The carotid IMT was measured as the...
distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line using computer software (Intima-scope, Media Cross Inc., Tokyo, Japan). The maximum value of IMT including plaque lesions in the common carotid artery, the carotid bulb, and the internal carotid artery were measured separately, and the greatest value of them (max-IMT) was used as the representative value for each individual.

**Definitions**

Hemoglobin A1c levels were converted to a National Glycohemoglobin Standardization Program equivalent value with the conversion equation reported by the Japan Diabetes Society. LDL cholesterol levels were calculated from total cholesterol, high-density cholesterol, and triglycerides levels according to the Friedewald’s formula. Retinopathy was defined as pre-proliferative or proliferative diabetic retinopathy, or history of photocoagulation or vitreous surgery due to diabetic retinopathy. Cardiovascular disease included ischemic heart disease with and without revascularization and stroke with and without symptoms and aftereffects.

**Statistical Analysis**

The impact of risk factors on ba-PWV and max-IMT was assessed using the linear mixed model. The standardized values of ba-PWV and max-IMT were treated as the dependent variable in a common model, in which the indication of the outcome (i.e., either standardized ba-PWV or max-IMT) and a risk factor of interest were included as the fixed effects. Furthermore, to assess the difference in the impact of the risk factor between the two outcomes, an interaction term between the indication of the outcome and the risk factor was additionally entered as the fixed effect in the model. If the null hypothesis that the regression estimate of the interaction term equaled to zero was statistically denied, the impact of the risk factor was considered significantly different between the outcomes. The unadjusted regression estimate of the risk factor to each outcome was obtained in this “univariate” model.

The adjusted regression estimate of each risk factor was subsequently calculated according to the “multivariate” model in which all the risk factors of interest were simultaneously entered. The risk factors included in the model were age, sex, smoking status, diabetic duration, hemoglobin A1c, treatment with oral hypoglycemic agents, treatment with insulin injection, systolic blood pressure, medication for hypertension, LDL cholesterol, HDL cholesterol, triglycerides, medication for hyperlipidemia, retinopathy, and cardiovascular disease. The risk factors that had a significant interaction effect in the preceding univariate model were again accompanied by their interaction term with the indication of the outcome in this multivariate model. On the other hand, the risk factors without any significant interaction effect in the preceding univariate model were considered to have a similar impact on ba-PWV and max-IMT. They were therefore treated without their interaction term in the multivariate model, to obtain their common adjusted regression estimates to the outcomes.

Since the dependent variables of the current models were already standardized (i.e., the standardized values of ba-PWV and max-IMT), the standardized regression estimate of a fixed effect $\beta$ was obtained by further dividing the regression estimate by the standard deviation (SD) of the fixed effect; $\beta$ represents the increment of the standardized outcomes per one-SD increase of the fixed effect.

Data are given as the mean ± SD for continuous variables and as percentages for dichotomous variables, if not otherwise mentioned. The triglycerides levels were expected to be right-skewed and therefore were log-transformed in the model analysis. A $p$ value of less than 0.05 was considered to be significant and 95% confidence intervals (CI) were given when required. All statistical analyses were performed using R software Program version 3.1.0 (R Development Core Team).

**Results**

The clinical characteristics of the study population are shown in Table 1. The mean age was 60 ± 11 years and 64% were men. The ba-PWV and max-IMT values were significantly correlated with each other (Pearson’s correlation coefficient $r=0.365$, $p<0.001$). Diabetic duration was not correlated with LDL or HDL cholesterol levels ($r=0.030$ and $-0.018$ and $p=0.225$ and 0.477, respectively).

According to the univariate analysis, sex, age, treatment with insulin injection, systolic blood pressure, medication for hypertension, LDL cholesterol, HDL cholesterol levels, and antiplatelet therapy showed a significantly different impact on ba-PWV compared to max-IMT $(p<0.05)$, whereas the other factors did not (Table 2). The subsequent multivariate model revealed that a significant difference was still observed in the impact of age, systolic blood pressure, LDL cholesterol, and HDL cholesterol on the outcomes (Table 3). As Table 3 shows, an older age was associated with the increase of ba-PWV ($\beta=0.443 [95\%$
CI: 0.397 to 0.488]) and max-IMT ($\beta=0.347$ [95% CI: 0.301 to 0.392]), but its impact was significantly greater on ba-PWV compared to max-IMT, with the difference of $\beta$ equal to 0.096 [95% CI: 0.038 to 0.154]. Similarly, a higher systolic blood pressure was associated with the increase of ba-PWV and max-IMT, but its impact was significantly greater on ba-PWV compared to max-IMT. On the other hand, a higher LDL cholesterol level and a lower HDL cholesterol level were independently associated only with a greater max-IMT and not with a greater ba-PWV. Male sex had a significant impact on both ba-PWV and max-IMT and there was no significant difference between the outcomes. Diabetic duration, hemoglobin A1c, retinopathy, and cardiovascular disease were also common independent risk factors of increased ba-PWV and max-IMT (Table 3).

The current findings indicate that age, systolic blood pressure, and the LDL and HDL cholesterol levels contribute to the discrepancy between ba-PWV and max-IMT. Patients with an old age with an elevated systolic blood pressure are therefore likely to have a higher ba-PWV even if their max-IMT is not elevated. On the other hand, those with an increased LDL cholesterol level and a decreased HDL cholesterol level are likely to have a higher max-IMT even if their ba-PWV is not elevated. Indeed, as shown in Fig. 1, these respective risk factors were associated with an increased prevalence of high ba-PWV in patients with low max-IMT, and high max-IMT in patients with low ba-PWV.

Finally, we performed a supplementary analysis to investigate whether the association of LDL and HDL cholesterol with max-IMT, rather than ba-PWV, would be similarly observed even after the study population was stratified by medication for hyperlipidemia. Consequently, the difference in $\beta$ of LDL cholesterol between ba-PWV versus max-IMT was -0.091 [95% CI: -0.145 to -0.036] in patients without medication and -0.060 [95% CI: -0.136 to -0.016] in patients with medication (both $p<0.05$). The intergroup difference in the $\beta$ differences was 0.030 [95% CI: -0.024 to 0.085], indicating that there was no significant difference between subgroups with and without medication. Similarly, the difference in $\beta$ of HDL cholesterol between ba-PWV and max-IMT was 0.094 [95% CI: 0.039 to 0.148] in patients without medication and 0.091 [95% CI: 0.017 to 0.166] in patients with medication (both $p<0.05$). The intergroup difference in the $\beta$ differences was -0.003 [95% CI: -0.057 to 0.051], indicating that there was no significant difference between subgroups with and without medication.

### Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Male (%)</th>
<th>Age (years)</th>
<th>Smoking (%)</th>
<th>Diabetic duration (years)</th>
<th>Hemoglobin A1c (%)</th>
<th>Treatment with oral hypoglycemic agents</th>
<th>Treatment with insulin injection</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Medication for hypertension</th>
<th>LDL cholesterol (mg/dL)</th>
<th>HDL cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Medication for hyperlipidemia</th>
<th>Retinopathy</th>
<th>Cardiovascular disease</th>
<th>Antiplatelet therapy</th>
<th>max-IMT (mm)</th>
<th>ba-PWV (cm/sec)</th>
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<td></td>
<td>1648</td>
<td>1053 (64%)</td>
<td>60 ± 11</td>
<td>883 (51%)</td>
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<td>7.2 ± 1.2</td>
<td>1136 (69%)</td>
<td>512 (31%)</td>
<td>132 ± 17</td>
<td>724 (44%)</td>
<td>105 ± 24</td>
<td>59 ± 16</td>
<td>99 (70, 142)</td>
<td>666 (40%)</td>
<td>103 (6%)</td>
<td>417 (25%)</td>
<td>413 (25%)</td>
<td>103 (6%)</td>
<td>1617 ± 294</td>
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Data are the mean ± SD or n (%), except for the triglycerides levels, which are shown as the median (1st and 3rd quartiles).

### Discussion

The current findings indicate that some cardiovascular risk factors have a different impact on arterial stiffness versus arterial wall thickness in Japanese diabetic patients, whereas others have a comparable impact on the two atherosclerotic aspects. Age and systolic blood pressure were more strongly associated with ba-PWV than with max-IMT, whereas a higher LDL cholesterol level and a lower HDL cholesterol level were independently associated only with a greater max-IMT and not with a greater ba-PWV. On the other hand, sex, diabetic duration, hemoglobin A1c levels, the presence of retinopathy, and cardiovascular disease were common independent risk factors of increased ba-PWV and max-IMT.

Previous studies suggested that the risk factors associated with arterial stiffness and wall thickness were not identical. However, those studies analyzed the association of risk factors with the two examinations separately and did not directly compare the impact of risk factors between the two examinations. In the current study, we succeeded in statistically demonstrating different impacts of cardiovascular risk factors on arterial stiffness assessed with ba-PWV and wall thickness assessed with max-IMT, by extending the linear mixed model.

The current findings indicated that higher LDL cholesterol...
Table 2. Unadjusted associations of the patients’ characteristics with the max-IMT and ba-PWV

<table>
<thead>
<tr>
<th>characteristic</th>
<th>max-IMT Unadjusted β</th>
<th>ba-PWV Unadjusted β</th>
<th>Difference (ba-PWV vs. max-IMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.058 [0.010, 0.106] *</td>
<td>-0.010 [-0.058, 0.038]</td>
<td>-0.068 [-0.123, -0.014] *</td>
</tr>
<tr>
<td>Age</td>
<td>0.407 [0.364, 0.449] *</td>
<td>0.535 [0.493, 0.578] *</td>
<td>0.128 [0.074, 0.182] *</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.045 [-0.004, 0.093]</td>
<td>0.024 [-0.024, 0.072]</td>
<td>-0.020 [-0.075, 0.034]</td>
</tr>
<tr>
<td>Diabetic duration</td>
<td>0.173 [0.125, 0.221] *</td>
<td>0.138 [0.091, 0.186] *</td>
<td>-0.035 [-0.089, 0.020]</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>-0.003 [-0.051, 0.045]</td>
<td>0.019 [-0.029, 0.068]</td>
<td>0.022 [-0.032, 0.077]</td>
</tr>
<tr>
<td>Treatment with oral hypoglycemic agents</td>
<td>0.121 [0.073, 0.168] *</td>
<td>0.163 [0.116, 0.211] *</td>
<td>0.043 [-0.012, 0.097]</td>
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<tr>
<td>Treatment with insulin injection</td>
<td>-0.025 [-0.073, 0.023]</td>
<td>0.041 [-0.007, 0.089]</td>
<td>0.066 [0.012, 0.120] *</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.189 [0.143, 0.235] *</td>
<td>0.392 [0.346, 0.438] *</td>
<td>0.204 [0.150, 0.257] *</td>
</tr>
<tr>
<td>Medication for hypertension</td>
<td>0.161 [0.114, 0.208] *</td>
<td>0.266 [0.218, 0.313] *</td>
<td>0.105 [0.051, 0.159] *</td>
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<tr>
<td>LDL cholesterol</td>
<td>0.071 [0.023, 0.119] *</td>
<td>-0.020 [-0.068, 0.028]</td>
<td>-0.091 [-0.145, -0.036] *</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.144 [-0.192, -0.096] *</td>
<td>-0.050 [-0.098, -0.001] *</td>
<td>0.094 [0.040, 0.148] *</td>
</tr>
<tr>
<td>Ln (Triglycerides)</td>
<td>0.042 [-0.006, 0.0090]</td>
<td>0.037 [-0.011, 0.086]</td>
<td>-0.005 [-0.059, 0.050]</td>
</tr>
<tr>
<td>Medication for hyperlipidemia</td>
<td>0.048 [0.000, 0.096]</td>
<td>0.061 [0.013, 0.110] *</td>
<td>0.013 [-0.041, 0.068]</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.120 [0.072, 0.168] *</td>
<td>0.152 [0.104, 0.200] *</td>
<td>0.032 [-0.022, 0.086]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.264 [0.217, 0.311] *</td>
<td>0.269 [0.223, 0.316] *</td>
<td>0.005 [-0.049, 0.060]</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>0.171 [0.124, 0.218] *</td>
<td>0.238 [0.191, 0.285] *</td>
<td>0.067 [0.013, 0.121] *</td>
</tr>
</tbody>
</table>

Data are standardized regression estimates and their 95% confidence intervals, obtained from the univariate model. *p < 0.05.

Cholesterol levels and lower HDL cholesterol levels were associated with greater wall thickness rather than greater arterial stiffness. These findings were also suggested by previous reports. As accumulating evidence shows, LDL is a primary pro-atherogenic lipoprotein and its excess in blood leads to atheroma formation in the arterial wall. On the other hand, HDL works as anti-atherosclerotic lipoprotein; it is involved in cholesterol efflux from atheroma, leading to a reduced risk of atheromatous change within the arterial wall. The max-IMT values, rather than ba-PWV values, would reflect such a structural change.

On the other hand, the impact of age and systolic blood pressure were greater on ba-PWV than on max-IMT, although they were significantly associated with both ba-PWV and max-IMT. Previous studies suggested that age and hypertension were associated with both arterial stiffness and thickness. However, the difference of their clinical impact between arterial stiffness and thickness remained to be investigated. Hypertension alters biomechanical stimuli to the artery, promoting the structural change of the artery as well as affecting functional properties of the artery. Arterial stiffness reflects these two aspects. Although its biomechanical stimuli also promotes atherogenic changes, especially at branch points and curves, the current findings indicate that ba-PWV is more influenced by elevated blood pressure than max-IMT. It is reported that age-associated and hypertension-derived arterial changes have much in common, indicating that common signaling and pathways mediate those changes. The current observation of a greater impact of age on ba-PWV than max-IMT might reflect these pathophysiological backgrounds.

Unlike age, blood pressure and cholesterol levels, a patient’s diabetic duration, hemoglobin A1c levels, and presence of retinopathy had a similar impact on both ba-PWV and max-IMT. Given that these three variables can be considered as indicators of exposure of hyperglycemia, the burden of hyperglycemia would similarly affect arterial stiffness and wall thickness in type 2 diabetic patients. Similarly, male sex and history of cardiovascular disease demonstrated a similar impact on ba-PWV and max-IMT. These variables might not distinguish two aspects of atherosclerosis, i.e., arterial stiffness and wall thickness.

Although the current study was performed in a cross-sectional manner, the current findings might imply a therapeutic perspective on the prevention of atherosclerosis. That is, an intervention to normalize lipid profiles might have beneficial effects on the prevention of the structural change of the arterial wall rather than on arterial stiffness, whereas blood pressure control might be more important in preventing arterial stiffness than wall thickness. On the other hand, glycemic control might be beneficial for the
participant. Although this assessment was adopted in some previous studies, others assessed ba-PWV as the mean of the two measurements or the measurement on one specific side (e.g., the right side). Future studies will be needed to investigate whether similar findings would be obtained when these assessments were used instead of selecting the higher value.

Second, detailed data on smoking status, e.g., the amount and years of smoking, were not available in the current study. The simple assessment of smoking status as a discrete variable might attribute to the lack of significance in association with ba-PWV and max-IMT. Third, the current study was a cross-sectional design and therefore only revealed the association between the risk factors and ba-PWV and max-IMT. Whether these risk factors would elevate the ba-PWV and max-IMT remains to be investigated. Fourth, the current study did not evaluate the tissue characterization of plaque lesions in the carotid artery. An evaluation could discriminate the structural change of arterial wall and might provide more detailed information on the different impacts of cardiovascular risk factors on arterial stiffness versus wall thickness. Fifth, the current study did not assess patient medications in detail and therefore might have overlooked possible pleiotropic effects of individual medications. Sixth, only Japanese diabetic patients were included in the current study. Some studies have indicated ethnic differences.

In the current study, triglycerides levels were not significantly associated with any markers of atherosclerosis. On the other hand, the Japan Diabetes Complication Study (JDCS) reported that triglycerides levels are major risk factors for the future risk of coronary heart disease in type 2 diabetic patients, suggesting an important association of triglycerides levels with atherosclerosis. Although the distribution of triglycerides levels in the current study did not seem so different from that in the JDCS, an increasing trend in triglycerides levels has been recently reported. Future studies including more patients with elevated triglycerides levels might be needed to discuss the association of triglycerides levels with arterial stiffness and wall thickness.

The current study is associated with some limitations. First, arterial stiffness was evaluated by ba-PWV and not by other examinations such as carotid-femoral PWV. Although previous reports demonstrated a good correlation between ba-PWV and carotid-femoral PWV, it remains unknown whether the use of carotid-femoral PWV would demonstrate similar findings. In addition, the current study collected the ba-PWV data by selecting the higher value of the two ba-PWV readings on the right and left sides from each participant. Although this assessment was adopted in some previous studies; others assessed ba-PWV as the mean of the two measurements or the measurement on one specific side (e.g., the right side). Future studies will be needed to investigate whether similar findings would be obtained when these assessments were used instead of selecting the higher value. Second, detailed data on smoking status, e.g., the amount and years of smoking, were not available in the current study. The simple assessment of smoking status as a discrete variable might attribute to the lack of significance in association with ba-PWV and max-IMT. Third, the current study was a cross-sectional design and therefore only revealed the association between the risk factors and ba-PWV and max-IMT. Whether these risk factors would elevate the ba-PWV and max-IMT remains to be investigated. Fourth, the current study did not evaluate the tissue characterization of plaque lesions in the carotid artery. An evaluation could discriminate the structural change of arterial wall and might provide more detailed information on the different impacts of cardiovascular risk factors on arterial stiffness versus wall thickness. Fifth, the current study did not assess patient medications in detail and therefore might have overlooked possible pleiotropic effects of individual medications. Sixth, only Japanese diabetic patients were included in the current study. Some studies have indicated ethnic dif-

### Table 3. Adjusted associations of patients’ characteristics with max-IMT and ba-PWV

<table>
<thead>
<tr>
<th></th>
<th>max-IMT Adjusted $\beta$</th>
<th>ba-PWV Adjusted $\beta$</th>
<th>Difference (ba-PWV vs. max-IMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.093 [0.046, 0.140] *</td>
<td>0.057 [0.010, 0.105] *</td>
<td>-0.036 [-0.090, 0.019]</td>
</tr>
<tr>
<td>Age</td>
<td>0.347 [0.301, 0.392] *</td>
<td>0.443 [0.397, 0.488] *</td>
<td>0.096 [0.038, 0.154] *</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.006 [-0.031, 0.044]</td>
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<tr>
<td>Diabetic duration</td>
<td>0.084 [0.053, 0.116] *</td>
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</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>0.051 [0.019, 0.084] *</td>
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</tr>
<tr>
<td>Treatment with oral hypoglycemic agents</td>
<td>0.024 [-0.007, 0.055]</td>
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</tr>
<tr>
<td>Treatment with insulin injection</td>
<td>-0.009 [-0.053, -0.034]</td>
<td>0.038 [-0.005, 0.082]</td>
<td>0.048 [-0.007, 0.102]</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.090 [0.048, 0.133] *</td>
<td>0.277 [0.234, 0.320] *</td>
<td>0.187 [0.131, 0.243] *</td>
</tr>
<tr>
<td>Medication for hypertension</td>
<td>0.030 [-0.014, 0.073]</td>
<td>0.061 [0.018, 0.105] *</td>
<td>0.031 [-0.025, 0.088]</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.078 [0.037, 0.119] *</td>
<td>-0.016 [-0.056, 0.025]</td>
<td>-0.094 [-0.147, -0.040] *</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.079 [-0.123, -0.035] *</td>
<td>0.018 [-0.026, 0.063]</td>
<td>0.097 [0.043, 0.152] *</td>
</tr>
<tr>
<td>Ln (Triglycerides)</td>
<td>-0.001 [-0.036, 0.033]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Medication for hyperlipidemia</td>
<td>0.021 [-0.010, 0.053]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.083 [0.052, 0.114] *</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.073 [0.039, 0.107] *</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>-0.005 [-0.049, 0.040]</td>
<td>0.003 [-0.041, 0.048]</td>
<td>0.008 [-0.049, 0.065]</td>
</tr>
</tbody>
</table>

The data are standardized regression estimates and their 95% confidence intervals, which are obtained from the multivariate model. *$p<0.05$. 

Prevention of both arterial stiffness and wall thickness. Future clinical trials are needed to prove this hypothesis.
Fig. 1. The prevalence of high max-IMT in patients with low ba-PWV (A) and the prevalence of high ba-PWV in patients with low max-IMT (B).

A: Patients with the lowest quartile of ba-PWV (≤ 1405 cm/s) were classified according to the number of the following risk factors for increased max-IMT: an increased LDL cholesterol level (defined as its highest quartile, i.e., ≥ 121 mg/dL) and a decreased HDL cholesterol level (defined as its lowest quartile, i.e., ≤ 47 mg/dL). The data show the prevalence of the highest quartile of max-IMT (≥ 1.18 mm) and its 95% CI as estimated by the Clopper-Pearson's method.

B: Patients with the lowest quartile of max-IMT (≤ 0.86 mm) were classified according to the number of the following risk factors for increased ba-PWV: an old age (defined as its highest quartile, i.e., ≥ 69 years) and an elevated systolic blood pressure (defined as its highest quartile, i.e., ≥ 144 mmHg). The data show the prevalence of the highest quartile of ba-PWV (≥ 1803 sm/s) and its 95% CI as estimated by the Clopper-Pearson's method.

Conclusions

The impact of cardiovascular risk factors on elevated ba-PWV and max-IMT was not identical in Japanese type 2 diabetic patients. LDL and HDL cholesterol levels were more associated with max-IMT, whereas age and blood pressure were more associated with ba-PWV. On the other hand, sex, diabetic duration, hemoglobin A1c levels, and the presence of retinopathy and cardiovascular disease had a similar impact on PWV and IMT.

Conflicts of Interest

There are no conflicts of interest associated with this manuscript.

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