

# Combination of the Framingham Risk Score and Carotid Intima-Media Thickness Improves the Prediction of Cardiovascular Events in Patients With Type 2 Diabetes

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**OBJECTIVE**—The aim of this study was to investigate whether carotid intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) add value to the Framingham risk score (FRS) in predicting the development of cardiovascular diseases (CVDs) in type 2 diabetic patients with a negative history of CVD.

**RESEARCH DESIGN AND METHODS**—Type 2 diabetic patients ( $n = 783$ ) were retrospectively recruited and followed for CVD.

**RESULTS**—During a 5.4-year follow-up period, 85 incidences of CVD were recorded (10.9%). After adjustment for conventional arterial risk factors, multivariate analysis with the Cox proportional hazards model identified IMT, but not baPWV, as a significant determinant of CVD. In addition, the combination of FRS with IMT, but not with baPWV, improved the prediction of CVD.

**CONCLUSIONS**—Carotid IMT is a significant predictor of CVD in asymptomatic type 2 diabetic patients, and the combination of FRS and IMT improves the prediction of CVD in these patients.

*Diabetes Care* 35:178–180, 2012

Identification of patients with a high probability of developing cardiovascular diseases (CVDs) is important for efficient treatment of type 2 diabetes. Although the Framingham risk score (FRS) is considered a useful tool for quantitative assessment of the risk for CVD in the general populations (1,2), the score does not have sufficient power to predict future onset of CVD in type 2 diabetic patients (3–5).

In the current study, we first determined the incidence of CVD in a cohort of

patients with type 2 diabetes and then compared the prediction of CVD by FRS alone, the combination of FRS with carotid intima-media thickness (IMT), and the combination of FRS and brachial-ankle pulse wave velocity (baPWV).

## RESEARCH DESIGN AND METHODS

### Subjects

We screened 1,538 consecutive type 2 diabetic patients (1,025 men and 513 women)

who attended Juntendo University Hospital on a regular basis and had undergone a measurement of IMT and baPWV between 2003 and 2005 at the outpatient clinic. Among them, we selected those with the following criteria: 1) diagnosed with type 2 diabetes, 2) 30–75 years of age, and 3) negative history of CVD. Patients with renal dysfunction, severe liver disease, and malignancy were excluded. The hospital ethics committee approved the study protocol, and informed consent was obtained from each subject.

### Data acquisition

Blood pressure (BP) and BMI were determined at baseline. Blood samples were obtained after an overnight fast. The 10-year coronary risk was estimated using FRS (6).

CVD, including cardiovascular death, nonfatal myocardial infarction, unstable angina, stable angina, transient ischemic attack, and ischemic stroke, was registered during the 5–6-year follow-up period.

### Measurements of IMT and baPWV

The mean IMT of the common carotid artery, including plaque, was measured by ultrasonography using the method described previously (7–9). baPWV was measured using an automatic waveform analyzer as described previously (8).

### Statistical analysis

The baseline data (recorded at study entry) of the different groups were compared by the unpaired Student  $t$  test, Mann-Whitney  $U$  test, or  $\chi^2$  test, as appropriate (JMP version 9.0.0; SAS Institute Inc., Tokyo, Japan). Prediction of CVD at the end of the 5–6-year follow-up period was evaluated by comparing receiver operating characteristic (ROC) curves. The cumulative event-free rates were estimated from Kaplan-Meier survival curves and differences were tested by the log-rank test. The Cox proportional hazards model was used to identify independent predictors of primary CVD.

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Received 15 July 2011 and accepted 23 September 2011.

DOI: 10.2337/dc11-1333

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Classical atherosclerotic risk factors and markers such as age, sex, BMI, systolic BP, HbA<sub>1c</sub>, total cholesterol, HDL cholesterol, triglyceride, smoking, baPWV, and carotid artery IMT were assessed as independent variables for modeling. All statistical tests were two-sided with a 5% significance level.

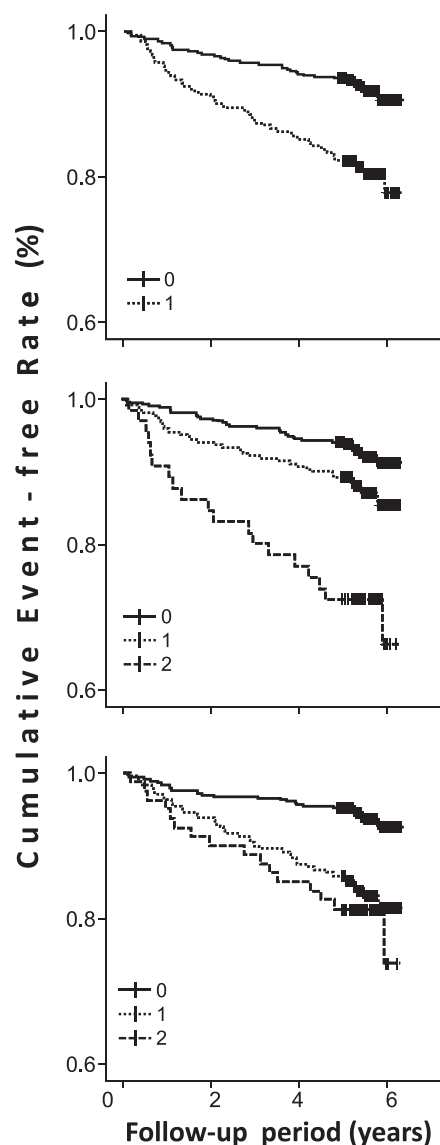
**RESULTS**—At baseline, 783 patients were recruited for the evaluation. During the follow-up period ( $5.46 \pm 0.39$  years), 50 coronary events and 35 strokes were recorded. These patients were older and had higher systolic and diastolic BP, higher baPWV, higher IMT, and higher FRS, compared with those without such events. CVD occurred more frequently in men than in women.

The Kaplan-Meier curves showed lower event-free rates with higher IMT (using the fourth quintile of IMT as the cutoff value; log-rank  $\chi^2 = 8.87$ ;  $P = 0.03$ ), baPWV (using the fourth quintile of baPWV as the cutoff value; log-rank  $\chi^2 = 9.83$ ;  $P = 0.02$ ), and Framingham score (FRS  $\leq 10\%$ , FRS  $>10\%$  but  $\leq 20\%$ , FRS  $>20\%$ ; log-rank  $\chi^2 = 23.1$ ;  $P > 0.001$ ).

Next, we examined the ability to predict CVD at  $\sim 5$  years by evaluating ROC. The areas under the ROC curves for IMT and baPWV were similar (0.590 and 0.583, respectively), although that for FRS was modestly higher (0.645). Simple addition of both IMT and baPWV to FRS results in only a modest increase of the area under the ROC curve (0.656 and 0.655, respectively). Multivariate analysis using the Cox proportional hazards model identified age (relative risk per 1 SD [RR], 1.06; 95% CI 1.03–1.10,  $P < 0.001$ ), sex (RR for women, 0.50; 0.27–0.92,  $P = 0.03$ ), and carotid IMT (2.39; 1.19–4.81,  $P = 0.02$ ) as independent predictors for CVD.

We also investigated whether the combination of FRS and high IMT or baPWV had a greater predictive power for CVD than FRS alone. The Kaplan-Meier curves showed a low cumulative event-free rate with the combination of FRS and IMT (log-rank  $\chi^2 = 31.4$ ;  $P < 0.001$ ), but not with baPWV (log-rank  $\chi^2 = 26.2$ ;  $P < 0.001$ ) (Fig. 1).

**CONCLUSIONS**—The incidence of CVD in type 2 diabetic patients is rising in Japan. In fact, the CVD event rate in our subjects was higher than that reported in a previous study (10). Thus, it is important to identify patients at high risk for



**Figure 1**—CVD event-free rate according to FRS (top), FRS combined with carotid IMT (middle), and FRS combined with baPWV (bottom). Group 0 represents patients with low and intermediate FRS and those with first to third quintile IMT and baPWV values. Group 1 represents patients with high FRS and those with fourth quintile IMT and baPWV values. Categorical variables of 0, 1, and 2 were used for the combined index of carotid IMT plus FRS and FRS plus baPWV.

developing such events in order to reduce morbidity and mortality.

The estimated cumulative rate of CVD for the highest quintile of IMT and that of baPWV confirmed its relationship with the respective high incidence of primary CVD. Prediction of CVD improved with the combination of FRS and IMT, consistent with a previous small study (11), but not with the combination of FRS and

baPWV, compared with FRS alone. In this regard, Nomura et al. (12) reported that carotid IMT, but not baPWV, was an independent determinant of silent cerebral infarction in Japanese type 2 diabetic patients. Another study concluded that IMT was more useful than baPWV for prediction of coronary artery atherosclerosis in patients clinically suspected of having coronary heart disease (13). IMT and baPWV reflect two different aspects of atherosclerosis. Although the exact reason for the difference in their predictive power is not clear at present, IMT seems to have more power in predicting CVD than baPWV. However, further studies of larger sample size are needed.

Our study has certain limitations. First, the study was retrospective and included a relatively small sample size. Second, we evaluated only common carotid IMT including plaque; however, the use of different methods to measure IMT may yield different results.

In conclusion, the current study showed that IMT is an independent risk factor for CVD in asymptomatic type 2 diabetic patients and that the combination of FRS and high IMT, but not baPWV, has a greater predictive power of CVD events compared with FRS alone.

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

H.W. supervised and planned this work, contributed to the discussion, reviewed and edited the manuscript, and was principal investigator responsible for the contents of the article. M.Y. collected and analyzed data and wrote the manuscript. T.M. supervised and planned this work, contributed to the discussion, and reviewed and edited the manuscript. R.K. reviewed and edited the manuscript. R.Y. analyzed data. T.S., F.I., A.K., and C.O. wrote and reviewed the manuscript. T.H. analyzed the data and supervised this work.

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