OBJECTIVE—The aim of this study is to evaluate whether noninvasive ultrasonic tissue characterization of carotid plaque using integrated backscatter (IBS) analysis can be a predictor of future cardiovascular events (CVE) in asymptomatic type 2 diabetic patients.

RESEARCH DESIGN AND METHODS—We prospectively evaluated the association between Calibrated-IBS value, an ultrasonic marker for tissue characteristics of carotid plaque, and CVE in 85 asymptomatic type 2 diabetic patients with carotid plaque.

RESULTS—The median follow-up period was 7.9 years, and there were 20 new CVE. The risk of CVE was significantly higher in the subjects with low Calibrated-IBS values (< −17.1 dB; n = 42) as compared with those with high values (≥ −17.1 dB; n = 43) (P = 0.004, log-rank test). Cox proportional hazards regression analysis revealed that both Calibrated-IBS value (hazard ratio [HR] 0.802 [95% CI 0.710–0.902]; P = 0.0001) and plaque thickness (1.938 [1.170–3.213]; P = 0.010) were independently associated with CVE, even after adjustment for the 10-year risk for a general cardiovascular disease estimated by Framingham risk scoring (FRS). Time-dependent receiver operating characteristic curve analysis for CVE at 10 years after the baseline examinations revealed that area under the curve for Calibrated-IBS was 0.76 (0.60–0.90) and substantially higher than those for plaque thickness (0.60 [0.45–0.79]) and FRS (0.60 [0.40–0.78]). These analyses also revealed that the addition of both plaque thickness and Calibrated-IBS value to conventional risk factors significantly improved the event prediction.

CONCLUSIONS—Calibrated-IBS value could improve the risk prediction of CVE in asymptomatic type 2 diabetic patients with carotid plaque.
RESEARCH DESIGN AND METHODS

Subjects and selection criteria
The current study was a prospective cohort study conducted from October 1997 to January 2011 in Osaka Police Hospital in Japan. The prespecified primary outcome was the first occurrence of a cardiovascular event during the follow-up period. Middle-aged and older Japanese T2DM subjects with carotid plaque but without apparent CVD participated in this study. We considered subjects eligible when they fulfilled the following criteria: 1) age between 45 and 85 years at the time of enrollment; 2) diagnosis of T2DM based on Japan Diabetes Society’s criteria; 3) with carotid plaque diagnosed by ultrasonography; 4) without history of coronary heart disease (CHD) and cerebral infarction; and 5) without malignancy, connective tissue disease, and severe liver or renal dysfunction. Screening of the study subjects was performed consecutively during a 4-year period (from October 1997 to September 2001) at the outpatient clinics of diabetes in Osaka Police Hospital, where almost all of the T2DM patients were routinely subject to the carotid ultrasound screenings. Patients who met eligibility criteria were randomly asked if they could participate in the current study, and all of the patients who agreed to participate were registered. A total of 85 patients (males, 64.7%; age 63.1 ± 8.6 years [mean ± SD]) were enrolled. Because the number of the subjects included was less than intended, the follow-up period was prolonged to 10 years.

Assessment of cardiovascular and metabolic risk factors
The laboratory data and blood pressure measurements for the prior 6 months were collected and averaged. Blood pressure was measured at rest with a mercury sphygmomanometer. Fasting blood was withdrawn for analyses of serum total cholesterol, serum HDL-cholesterol, serum triglycerides, plasma glucose, and HbA1c levels by standard laboratory techniques. A structured questionnaire was used to determine medical history, current medication use, and smoking status. We used Framingham risk scoring (FRS) to derive the 10-year risk for a general CVD for men and women based on the Framingham Heart Study. FRS uses participant age, sex, total cholesterol, HDL-cholesterol, smoking status, presence of diabetes, systolic blood pressure, and use of antihypertensive agents among individuals to assign points. The precise categories for each variable and the point scoring system that we used have been published elsewhere (19). The UK Prospective Diabetes Study Risk Engine (URE), which estimates CHD risk using conventional risk factors such as age, sex, smoking, systolic blood pressure, total cholesterol, HDL-cholesterol, plus the diabetes-specific factors duration of diabetes and HbA1c, was also used as a model for predicting risk of CVE (20).

Ultrasound examination of carotid plaque
In this study, localized elevated lesions with maximum thickness of >1 mm, having a point of inflection on the surface of intima-media complex, were defined as carotid plaque based on the Japanese Society of Ultrasonics in Medicine’s guideline (21). Ultrasound examination of the carotid artery was performed by two expert sonographers with the SONOS 5500 (Philips Medical Systems) using an electrical linear transducer (midfrequency of 7.5 MHz) at the beginning of the observation period. The detection limit of this system was ~0.1 mm. Initially, conventional B-mode imaging of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery was performed bilaterally in three different longitudinal projections (anterior, lateral, and posterior, which corresponded to ~60, 90, 150° for the right carotid artery and ~210, 270, and 300° for the left carotid artery marked on the Meijer’s Arc) as well as transverse projections, and the plaque thickness was measured at the maximally thick point at the border with the vascular lumen and the adventitial layer. In cases with multiple plaques, only the thickest plaque was chosen for IBS analysis.

IBS analysis of carotid plaque was performed with a software package Acoustic Densitometry with the SONOS 5500 (Philips Medical Systems). In this system, the return echoes that impinge on the individual elements of the transducer are amplified, mixed to the intermediate frequency signal, and sent to either a standard ultrasound video-processing chain for the B-mode image or a special IBS processor. In the IBS image, the gray level is displayed in proportion to the IBS power, which is calibrated in dB and has a dynamic range of 64 dB. Thus, IBS is calculated as the average power of the ultrasonic backscattered signal from a region of interest (ROI) and represents its tissue structure (15,16). IBS data in the intima-media complex and those in the adventitia were sampled at the thickest plaque. We placed the rectangular-shaped ROIs (1.0 × 0.1 mm) in a line from the leading edge of the first echogenic line to the leading edge of the second echogenic line of the thickest site and measured the IBS values of these ROIs. We defined the average of these IBS values as the IBS value in intima-media complex. Similarly, we measured the IBS value in the adventitia. According to a previous report, the relative IBS values of the adventitia in pathologically different samples were almost the same, and thus atherosclerotic change has been considered to occur mainly in the intima-media complex of the carotid artery wall (15). Therefore, the IBS values in the intima-media complex were calibrated by subtracting the IBS values in the adventitia as follows:

Calibrated-IBS = IBS values in intima-media complex – IBS values in the adventitia

In this way, the Calibrated-IBS has been considered to be a parameter that likely reflects the tissue characteristics of the intima-media complex.

All scans were conducted by two expert sonographers and read by a single reader, and all of them were unaware of the clinical characteristics of the subjects. The intraobserver and interobserver variabilities of the IBS values (± SE) were 3.2 ± 0.4 and 3.5 ± 0.4%, respectively.

CVE
The prespecified primary outcome was the first occurrence of a CVE, which was a composite of any CHD event (myocardial infarction, angina, and CHD death) and any ischemic stroke (fetal and nonfatal ischemic stroke) during the follow-up period. The diagnosis of the occurrence of CHD event was performed by cardiologists based on the clinical symptoms, characteristic electrocardiogram changes, cardiac enzyme levels, and the findings in coronary angiography and/or echocardiography, according to established guidelines. An ischemic stroke event was defined as a validated definite or probable hospitalized atherothrombotic, cardioembolic, lacunar, and other type ischemic strokes diagnosed by neurosurgical experts based on clinical symptoms and neuroimaging findings, according to the National Institute of Neurologic Disorders and Stroke III classification. All patients were followed up at each hospital visit or by telephone, if necessary, and the occurrence of medical events was determined. For potential new CVE,
Carotid plaque and cardiovascular events

additional information, including the results of imaging and other diagnostic procedures, were obtained for confirmation, and all causes of death were confirmed by hospital records.

For participants with incident CVE, follow-up was defined as the period between the baseline clinic visit and the date of the first CVE. For participants with no CVE, follow-up continued until the date of death or January 2011 or until the date of last contact. Patients were allowed to use any concurrent treatment.

Statistical analysis
Data are given as means and SDs for continuous variables or as percentages for dichotomous variables. The occurrence of CVE was plotted using the Kaplan-Meier method, and the differences among the three groups were assessed by a log-rank test. The multivariate Cox proportional hazards regression model was used to determine the adjusted association of each variable with the outcome. Hazard ratios (HRs) and 95% CIs are reported. A P value <0.05 was considered significant. The ability of variables to predict the occurrence of CVE was examined by time-dependent receiver operating characteristic (ROC) curve analyses (22).

These statistical analyses were performed using SPSS version 15.0J (SPSS, Chicago, IL).

RESULTS

Association between Calibrated-IBS and CVE in subjects with T2DM
The baseline characteristics are shown in Table 1. The median follow-up period was 7.9 years, and there were 20 new CVE (14 CHD events and 6 ischemic strokes). First, to analyze the relationship between Calibrated-IBS level and the risk for CVE, we divided study subjects into two groups based on the median of Calibrated-IBS values (the subjects with low [≤1.7 dB] Calibrated-IBS values [n = 42] and those with high [≥1.7 dB] Calibrated-IBS values [n = 43]) and constructed Kaplan-Meier curves. During the follow-up period, 15 patients (35.7%) developed CVD events in the low Calibrated-IBS group and 5 (11.6%) in the high Calibrated-IBS group. As shown in Fig. 1A, the risk of CVE was significantly higher in the subjects with low Calibrated-IBS values as compared with those with high Calibrated-IBS values (P = 0.004, log-rank test). Similarly, to analyze the relationship between plaque thickness and the risk for CVE, we divided study subjects into two groups: subjects with large (>1.3 mm; n = 43) and small plaque thickness values (≤1.3 mm; n = 42). Although the risk for CVE was relatively higher in the subjects with large plaque thickness values as compared with those with small ones, it did not reach statistical significance (P = 0.148, log-rank test) (Fig. 1B).

To demonstrate that Calibrated-IBS value is a determinant of the occurrence of CVE independent of the FRS and plaque thickness, we also performed a multivariate Cox proportional hazards regression analysis and found that both Calibrated-IBS value (HR 0.802 [95% CI 0.710–0.906]; P < 0.0001) and plaque thickness (1.938 [1.170–3.213]; P = 0.010) were independently associated with CVE, even after adjustment for the 10-year risk for a general CVD estimated by FRS. Similarly, another multivariate Cox proportional hazards regression analysis showed that both Calibrated-IBS value (0.808 [0.715–0.913]; P = 0.0001) and plaque thickness (1.988 [1.218–3.246]; P = 0.006) were independently associated with CVE, even after adjustment for URE that provides the CHD risk estimates in T2DM subjects.

Contribution of Calibrated-IBS in the prediction of CVE in subjects with T2DM
Next, we examined the ability of variables to predict the occurrence of CVE by time-dependent ROC curve analyses. Time-dependent ROC curve analysis for CVE at 10 years after the baseline examinations revealed that area under the curve (AUC) for

Table 1—Baseline characteristics according to Calibrated-IBS levels

| Parameters                          | Total subjects (N = 85) | Low Calibrated-IBS (n = 42) | High Calibrated-IBS (n = 43) | P value |
|------------------------------------|------------------------|-----------------------------|-----------------------------|---------|
| **Sex (female/male)**              | 30/55                  | 15/27                       | 15/28                       | NS      |
| **Age (years)**                    | 63.1 ± 8.6             | 62.2 ± 7.6                  | 63.1 ± 9.5                  | NS      |
| **Duration of diabetes (years)**   | 12.3 ± 9.4             | 11.2 ± 7.0                  | 13.3 ± 11.1                 | NS      |
| **Smoking status [n (%)]**         | 31 (36.5)              | 14 (33.3)                   | 17 (39.5)                   | NS      |
| **BMI (kg/m²)**                    | 23.4 ± 2.7             | 23.6 ± 2.5                  | 23.3 ± 2.8                  | NS      |
| **HbA1c (%)**                      | 7.9 ± 1.6              | 7.8 ± 1.6                   | 8.0 ± 1.7                   | NS      |
| **Systolic blood pressure (mmHg)** | 132 ± 14               | 132 ± 12                    | 132 ± 15                    | NS      |
| **Diastolic blood pressure (mmHg)**| 74 ± 11                | 73 ± 9                      | 76 ± 12                     | NS      |
| **Total cholesterol (mg/dL)**      | 205 ± 39               | 202 ± 38                    | 209 ± 40                    | NS      |
| **HDL-cholesterol (mg/dL)**        | 56 ± 15                | 53 ± 15                     | 59 ± 14                     | NS      |
| **Triglyceride (mg/dL)**           | 129 ± 62               | 137 ± 62                    | 122 ± 62                    | NS      |
| **LDL-cholesterol (mg/dL)**        | 124 ± 36               | 122 ± 37                    | 126 ± 36                    | NS      |
| **Using oral hypoglycemic agents** | 39 (45.9)              | 23 (54.8)                   | 16 (37.2)                   | NS      |
| **α-Glucosidase inhibitors**       | 9 (10.6)               | 5 (11.9)                    | 4 (9.3)                     | NS      |
| **Biguanides**                     | 7 (8.2)                | 3 (7.1)                     | 4 (9.3)                     | NS      |
| **Hiazoldinediones**               | 3 (3.5)                | 2 (4.8)                     | 1 (2.3)                     | NS      |
| **Sulfonylureas**                  | 32 (37.6)              | 18 (42.9)                   | 14 (32.6)                   | NS      |
| **Using insulin**                  | 11 (12.9)              | 2 (4.8)                     | 8 (18.6)                    | NS      |
| **Using statins**                  | 23 (27.1)              | 10 (23.8)                   | 13 (30.2)                   | NS      |
| **Using antihypertensive drugs**   | 26 (30.6)              | 13 (31.0)                   | 13 (30.2)                   | NS      |
| **ACEi or ARB**                    | 14 (16.5)              | 8 (19.0)                    | 6 (14.0)                    | NS      |
| **Calcium-channel blockers**       | 18 (21.2)              | 10 (23.8)                   | 8 (18.6)                    | NS      |
| **FRS 10-year estimated risk (%)**| 32 ± 15                | 32 ± 15                     | 31 ± 16                     | NS      |
| **Plaque thickness (mm)**          | 1.51 ± 0.60            | 1.49 ± 0.53                 | 1.53 ± 0.68                 | NS      |
| **Calibrated-IBS (dB)**            | −17.4 ± 3.9            | −20.5 ± 2.6                 | −14.3 ± 2.0                 | <0.0001 |

Data are shown as n (%) or mean ± SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
Calibrated-IBS was 0.76 (95% CI 0.60–0.90), which we considered satisfactory (because an AUC of 0.7–0.9 is generally believed to indicate a valid test). The AUC for Calibrated-IBS was substantially higher than those for plaque thickness (HR 0.60 [95% CI 0.45–0.79]), FRS (HR 0.60 [0.40–0.78]), and URE (HR 0.64 [0.41–0.83]), although there were not statistically significant differences.

Judging from the trend of the ROC curve, a Calibrated-IBS value of 0.78 dB can be considered a reasonable cutoff. When the cutoff for Calibrated-IBS value was set at 0.78 dB, the test identified T2DM patients who would develop CVE with a sensitivity of 93% and a specificity of 61%.

Next, to examine whether the addition of Calibrated-IBS and/or plaque thickness to conventional coronary risk factors could improve the prediction ability for CVE, time-dependent ROC curves were plotted. Although the addition of plaque thickness alone to FRS resulted in only a small increase in AUC (from 0.60 [95% CI 0.40–0.78] to 0.64 [0.45–0.81]), the addition of Calibrated-IBS to FRS substantially increased the AUC (from 0.60 [0.40–0.78] to 0.76 [0.61–0.89]). Furthermore, the addition of both plaque thickness and Calibrated-IBS to FRS significantly increased the AUC (from 0.60 [95% CI 0.40–0.78] to 0.83 [0.68–0.93]; P < 0.05) (Fig. 2A). Similar result was observed when we used URE instead of FRS: the addition of both plaque thickness and Calibrated-IBS to URE significantly increased the AUC (from 0.64 [0.41–0.83] to 0.81 [0.64–0.95]; P < 0.05) (Fig. 2B).

CONCLUSIONS—A large proportion of CVE in T2DM patients occurs in previously asymptomatic subjects and is often unanticipated. Such phenomena emphasize the necessity to close the gaps between the risk assessment with conventional risk factors and the real event risk. Atherosclerotic changes such as intima-media thickness thickening and plaque formation in the carotid artery, markers of early atherosclerosis and vascular remodeling that can be assessed quickly, noninvasively, and economically with high-resolution ultrasound, are correlated with conventional coronary risk factors and regarded as surrogates of CVD. Indeed, previous studies showed that CIMT was one of the independent predictors of CVD in asymptomatic subjects (5–8). However, previous studies indicated that the addition of CIMT to conventional coronary risk factors could bring, at most, only a small improvement of the prediction ability for CVD (9–11).

It is commonly accepted that lipid-rich plaques carry a higher risk of CVE because “disruption of a lipid-rich plaque” could play a crucial role in the development of CVE (23,24). Therefore, tissue characterization of a plaque lesion is considered to be useful for identifying subjects with a high risk for CVE. Recently, various modalities such as coronary computed tomography, magnetic resonance imaging, or fluorine-18-fluorodeoxyglucose positron emission tomography have been used to detect vulnerable plaque in coronary arteries and have shown relatively high accuracy. However, it is unrealistic to screen for individuals at high-risk for CVD with these tools in all diabetic patients, because these tests are limited by
the potential of significant adverse effects, technical difficulty, availability, and cost. Therefore, a noninvasive and inexpensive risk prediction tool has been required. Common carotid arteries as well as aortas are elastic arteries and prone to foam-cell formation at a very early age (25). Carotid bifurcation, which is situated in a transitional zone between elastic and muscular artery types, also develops foam-cell lesions and lipid core plaque at an early age. Interestingly, a recent study reported that the prevalence of lipid-rich plaques in carotid arteries was higher in coronary death than in noncoronary death (26). These findings lead us to a working hypothesis that the individuals who have lipid-rich plaques in their carotid arteries are prone to have lipid-rich plaques in their coronary and/or cerebral arteries, which will lead to CVE. Based on the above-described backgrounds, the current study evaluated whether noninvasive and inexpensive ultrasonic tissue characterization of carotid plaque using IBS analysis can provide any useful information for identifying subjects with a high risk for CVE.

Based on the prospective analysis in 85 asymptomatic T2DM patients with carotid plaque, we showed that subjects with low Calibrated-IBS value in carotid plaque had significantly higher risk for CVE. Furthermore, a multivariate Cox proportional hazards regression analysis revealed that Calibrated-IBS value was an independent predictor for CVE, even after adjustment for plaque thickness as well as the 10-year risk for a general CVD estimated by FRS or URE. These results were consistent with the findings of the previous studies showing that a low Calibrated-IBS in the carotid artery corresponded to atherosomatous plaque (14–17) and the idea that subjects with lipid-rich vulnerable plaque are prone to develop CVE.

In addition, time-dependent ROC curve analysis for CVE at 10 years after the baseline examinations revealed that AUC for Calibrated-IBS was substantially higher than those for plaque thickness, FRS, and URE, suggesting that Calibrated-IBS is potentially useful for identifying T2DM patients who will develop CVE. Judging from this analysis, a Calibrated-IBS value of $-17.8$ dB can be considered a reasonable threshold to identify high-risk subjects with a high sensitivity (93%) and a moderate specificity (61%), although it should be confirmed in further studies.

Time-dependent ROC curve analysis also revealed that the addition of both plaque thickness and Calibrated-IBS to FRS significantly improved the prediction of CVE, whereas the addition of plaque thickness alone to FRS made a marginal improvement. These findings suggested that the addition of ultrasonic tissue characterization of carotid plaque using IBS analysis to conventional measurement of plaque thickness could substantially improve the prediction ability for CVE in patients with carotid plaque. These results were compatible with a working hypothesis that assessment of tissue characteristics of carotid plaque as well as its size is useful for screening groups with a high risk of CVE.

Furthermore, it has been reported that the improvement of metabolic abnormalities by the administration of several drugs

![Figure 2](https://care.diabetesjournals.org)
(e.g., pioglitazone and statins) can favorably change the IBS values in coronary and carotid arteries (27–33), suggesting that this early vascular abnormality is the basis for earlier primary therapies in T2DM.

Our study has several limitations. First, the number of the study subjects was quite small, even though the current study had been originally designed as a pilot study. In fact, the number of the subjects included was less than intended, because we had difficulties in enrollment of eligible individuals in this study. Many candidates did not agree to participate because the schedule for the carotid assessment was rigid. This phenomenon may produce a selection bias, because those who agreed to enter this study may have had more concerns for their health for any reason. In addition, the actual number of the subjects included in the current study was 1/20 of the estimated number of the patients who met the eligibility criteria, which holds a certain risk of yielding some kind of selection bias. It is well-known that some types of selection biases spuriously increase the sensitivity and specificity of the diagnostic test.

Secondly, to establish the utility of the measurement of Calibrated-IBS values in daily clinical practice, another study with larger sample size should be performed. To conclusively demonstrate that Calibrated-IBS value is consistently and independently associated with CVE even after adjustment for conventional risk factors, several multivariate regression models should be also tested. For example, a multivariate Cox proportional hazards regression model including established confounding factors (e.g., age, sex, smoking, BMI, HbA1c, duration of diabetes, serum lipids, blood pressure, diabetes treatment, hypertension treatment, dyslipidemia treatment, or plaque thickness) as covariates simultaneously may be a good candidate. Unfortunately, we were not able to do such an analysis because the number of the study subjects in the current study was not large enough. To compensate for this shortcoming, we adopted FRS and URE scoring as risk-prediction estimates that reflect accumulative effects of these confounding factors. In addition, the stratified analysis according to the presence or extent of microvascular complications should be done because they are also predictors of CVD. The presence of calcified carotid plaques, as assessed by B-mode ultrasound, was also reported to be an independent predictor of vascular events, suggesting that the presence of calcified carotid plaques also serves as a marker of increased atherosclerotic risk. Although this approach is inferior to the measurement of Calibrated-IBS in quantitative capability, its convenience is of practical value. Therefore, it would be clinically worthwhile to evaluate whether the clinical utility of Calibrated-IBS is maintained even after the risk stratification using this approach. However, it was difficult for us to perform further stratified analyses because the subjects whose representative carotid plaques were classified as the calcified type were very few in number (n = 4).

Thirdly, the current study focused on the question whether measurement of Calibrated-IBS values can provide any useful information for identifying subjects with a high risk for CVE at a certain point in their long life with diabetes; it did not consider the changes in metabolic control and therapeutic regimen during the follow-up period, which affect both Calibrated-IBS values and the development of CVE. Therefore, whether longitudinal monitoring of Calibrated-IBS can add any beneficial information to the daily medical practice based on the monitoring of classic risk factors should be examined by further studies. Another prospective study needs to be performed to examine whether the risk stratification using Calibrated-IBS will lead to improved treatment decision making.

Finally, it is noted that the subjects of this study were Japanese T2DM patients with carotid plaque. It would thus be premature to generalize our findings to other races or ethnic groups, nondiabetic subjects, and subjects without carotid plaque.

Notwithstanding these limitations, our pilot study indicates that ultrasonic tissue characterization of carotid plaques using IBS analysis can provide useful information for identifying subjects with a high risk of CVE.

In conclusion, Calibrated-IBS value, a marker for tissue characteristics of carotid plaque that can be assessed quickly, noninvasively, and cheaply with ultrasound, can improve the risk prediction of CVE in asymptomatic T2DM patients with carotid plaque. A large-scale prospective study is needed to establish the usefulness of Calibrated-IBS as a predictive factor for the development of CVE in T2DM patients.

Acknowledgments—No potential conflicts of interest relevant to this article were reported. N.K. and H.K. researched data and wrote the manuscript. M.T., K.S., K.Y., Y.I., F.K., and T.K. researched data. Y.Y., K.K., and I.S. contributed to the discussion. All authors reviewed and approved the manuscript. N.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetess. Diabetologia 2001;44(Suppl. 2):S14–S21

2. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation 2006;113:2943–2946

3. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898–904

4. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003;290:891–897

5. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–1249

6. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–1437

7. O’Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wollson SK Jr. Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1990;340:14–22

8. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478–487

9. del Sol A1, Moons KG, Hollander M, et al. Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. Stroke 2001;32:1532–1538

10. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600–1607

11. Polak JF, Pencina MJ, Pencina KM, O’Donnell CJ, Wolf PA, D’Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011;365:213–221

12. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497

19. Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ. Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. Circulation 1991;83:1764–1770

14. Urbani MP, Picano E, Parenti G, et al. In vivo radiofrequency-based ultrasonic tissue characterization of the atherosclerotic plaque. Stroke 1993;24:1507–1512

15. Takuuchi S, Rakugi H, Honda K, et al. Quantitative ultrasonic tissue characterization can identify high-risk atherosclerotic alteration in human carotid arteries. Circulation 2000;102:766–770

16. Kawasaki M, Takatsu H, Noda T, et al. Noninvasive quantitative tissue characterization and two-dimensional color-coded map of human atherosclerotic lesions using ultrasound integrated backscatter: comparison between histology and integrated backscatter images. J Am Coll Cardiol 2001;38:486–492

17. Waki H, Masuyama T, Mori H, et al. Ultrasound tissue characterization of the atherosclerotic carotid artery: histological correlates or carotid integrated backscatter. Circ J 2003;67:1013–1016

18. Katakami N, Yamazaki Y, Kosugi K, et al. Tissue characterization identifies subjects with high risk of cardiovascular diseases. Diabetes Res Clin Pract 2004;63:93–102.

19. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497

20. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 36). Clin Sci (Lond) 2001;101:671–679

21. Terminology and Diagnostic Criteria Committee, Japan Society of Ultrasonics in Medicine. Subcommittee for Preparing Guidelines for Ultrasound Diagnosis of Carotid Artery. Standard method for ultrasound evaluation of carotid artery lesions. Jpn J Med Ultrasonics 2009;36:501–518

22. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–344

23. Davies MJ, Richardson PD, Woolf N, Katz DR, Munt J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J 1993;69:377–381

24. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006;47(Suppl):C7–C12

25. General findings of the International Atherosclerosis Project. Lab Invest 1968;18:498–502

26. Dalager S, Paaske WP, Kristensen KB, Laurberg JM, Falk E. Artery-related differences in atherosclerosis expression: implications for atherogenesis and dynamics in intima-media thickness. Stroke 2007;38:2698–2705

27. Hirano M, Nakamura T, Kita Y, et al. Rapid improvement of carotid plaque echogenicity within 1 month of pioglitazone treatment in patients with acute coronary syndrome. Atherosclerosis 2009;203:483–488

28. Inaba S, Okayama H, Funada JI, et al. Impact of type 2 diabetes on serial changes in tissue characteristics of coronary plaques: an integrated backscatter intravascular ultrasound analysis. Eur Heart J Cardiovasc Imaging 2012;13:717–723

29. Sugamura K, Sugiymama Y, Matsuzawa Y, Nozaki T, Horihata Y, Ogawa H. Benefit of adding pioglitazone to successful statin therapy in nondiabetic patients with coronary artery disease. Circ J 2008;72:1193–1197

30. Ito Y, Kawasaki M, Yokoyama H, et al. Different effects of pravastatin and cerivastatin on the media of the carotid arteries as assessed by integrated backscatter ultrasound. Circ J 2004;68:784–790

31. Katakami N, Sakamoto K, Kaneto H, et al. Lipid-lowering with atorvastatin improves tissue characteristics of carotid plaque. Atherosclerosis 2005;183:369–371

32. Yokoyama H, Kawasaki M, Ito Y, Minatoguchi S, Fujiwara H. Effects of fluvasatin on the carotid arterial media as assessed by integrated backscatter ultrasound compared with pulse-wave velocity. J Am Coll Cardiol 2005;46:2031–2037

33. Nakamura T, Ohta JE, Kita Y, et al. Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome. J Cardiovasc Pharmacol 2008;51:365–371