Incremental Predictive Value of Carotid Ultrasonography in the Assessment of Coronary Risk in a Cohort of Asymptomatic Type 2 Diabetic Subjects

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OBJECTIVE — Consensus guidelines recommend cardiovascular risk assessment as the initial step of primary prevention. The aim of this study was to evaluate the incremental predictive value for coronary events conferred by carotid ultrasonography in addition to risk assessment by Framingham score and screening for silent myocardial ischemia in a cohort of type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — We prospectively studied 229 patients free of any cardiovascular complication with at least one additional cardiovascular risk factor. At baseline, all patients had an exercise treadmill test, carotid intima-media thickness (IMT) measurement, and coronary risk assessment by Framingham score. Cardiovascular events were registered during a 5-year follow-up period.

RESULTS — Age, carotid IMT, carotid plaques, number of risk factors, Framingham score, and suboptimal exercise electrocardiogram were associated with incident cardiovascular events ($P < 0.05$). Carotid IMT was an independent predictor of cardiovascular events ($P = 0.045$). The predictive value for coronary events was similar for carotid IMT and Framingham score as assessed by area under the receiver operating characteristic curves. An improvement in risk prediction was conferred by addition of carotid IMT in a Cox model (global χ^2 increased from 14.1 to 18.1, $P = 0.035$).

CONCLUSIONS — This prospective study confirms that carotid IMT is a marker of cardiovascular risk in this type 2 diabetic cohort, establishes that carotid IMT provides a similar predictive value for coronary events than Framingham score, and suggests that the combination of these two indexes significantly improves risk prediction for these patients.

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Cardiovascular diseases are the main causes of death for diabetic patients (1). Coronary artery lesions are more extensive in diabetic patients, and coronary artery disease has a worse prognosis than in nondiabetic subjects (2). Moreover, silent myocardial ischemia, which is more frequent in diabetic patients than in the general population, can lead to delayed diagnosis and is associated with an increased risk of cardiac events (3–5).

Therefore, a strategy to efficiently reduce coronary morbidity and mortality in this high-risk population implies the capability to identify patients with the highest potential of developing coronary events. American and European guidelines recommend an office-based assessment as the initial step in predicting risk in primary prevention (6,7). This determination of coronary risk can be performed by a multifactorial statistical model such as Framingham risk scoring. Screening for silent myocardial ischemia is recommended when two or more additional risk factors are present (8). An exercise electrocardiogram test is often the first-line screening procedure and can yield prognostic information in both asymptomatic diabetic and nondiabetic men (5,9). Myocardial scintigraphy or a stress echocardiogram is additionally recommended if the exercise test is suboptimal (6,7). However, their predictive value is somewhat disappointing because the sensitivities of all these screening stress tests are low in asymptomatic populations (3).

A complementary approach might be to detect subclinical atherosclerosis in arterial sites that are easily accessible for noninvasive evaluation. Carotid intima-media thickness (IMT) measurement has been already used in epidemiologic and intervention studies as a surrogate index of atherosclerosis (10–11). Several studies have shown an association between increased carotid IMT and the incidence of cardiovascular disease in general population (12–15). Carotid IMT is significantly greater in diabetic patients than in nondiabetic subjects, and baseline carotid IMT predicted the incidence of nonfatal coronary heart disease in a small cohort of Japanese type 2 diabetic subjects (16–18). However, the predictive value of the combination of this surrogate marker of the arterial wall and the integration of con-

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Abbreviations: ETT, exercise treadmill test; IMT, intima-media thickness; ROC, receiver operating characteristic.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ventional cardiovascular risk factors has not been tested in type 2 diabetes.

The aim of this prospective study was to test the improvement in coronary risk prediction conferred by carotid arterial wall examination, in addition to assessing coronary risk by Framingham score and screening for silent myocardial ischemia by exercise stress testing in a cohort of asymptomatic type 2 diabetic patients with at least one additional cardiovascular risk factor.

RESEARCH DESIGN AND METHODS

— We report the results for 229 patients who completed the study with a 5-year follow-up. Patients were free of any cardiovascular complication, had no abnormalities on resting electrocardiogram, and had at least one additional cardiovascular risk factor. Inclusion criteria were age of 35–75 years; two oral glucose tolerance test results of either fasting glycemia >7.7 mmol/l or glycemia >11 mmol/l 2 h after an oral glucose tolerance test; and one additional cardiovascular risk factor, including antecedent of familial cardiovascular disease in first-degree relative <60 years for men and <65 years for women, arterial blood pressure >140/90 mmHg or treated hypertension, current smoking, microalbuminuria (≥30 mg/day), triglyceride level >2.3 mmol/l, HDL level <0.9 mmol/l, LDL level >4.1 mmol/l, or peripheral vascular disease (except stage IV). Exclusion criteria were type 1 diabetes or secondary diabetes; ketonuria; insulin therapy at baseline; severe microangiopathy (proliferative retinopathy, creatinemia >200 μmol/l); personal cardiovascular disease including previous myocardial infarction, angina pectoris, abnormal resting electrocardiogram, ischemic stroke, severe peripheral arteriopathy stage IV; and concomitant illness (hepatic insufficiency or neoplasia). All patients gave written informed consent before inclusion, and this study had the approval of our local ethics committee.

Demographic and clinical data were registered, including age, sex, antecedent of familial cardiovascular disease, BMI, smoking, and systolic and diastolic blood pressure with automatic measurement (mean of three determinations). Biological parameters were measured, including HbA_{1c}, lipid parameters (total cholesterol, HDL, and triglyceride levels), and microalbuminuria. A conventional resting 12-lead electrocardiogram was obtained (patients with abnormalities suggestive of coronary ischemia or with left bundle branch block were excluded). All patients had an exercise electrocardiogram test, and myocardial scintigraphy was also performed in the subgroup of patients with suboptimal exercise test. The absolute number of cardiovascular risk factors was recorded. The 10-year coronary risk was estimated by using Framingham risk scoring (19).

Cardiovascular events were registered during the 5-year follow-up period. Cardiovascular events included cardiovascular death, nonfatal myocardial infarction (abnormal cardiac enzymes levels with or without new ST-segment elevation >0.1 mV or apparition of Q-waves in at least two contiguous leads), unstable angina (hospitalization for angina pectoris occurring at rest and associated with electrocardiogram changes), stable angina (confirmed by abnormal exercise electrocardiogram and angiographically coronary stenosis), and ischemic stroke (defined as clinical and radiological evidence of stroke without intracranial hemorrhage).

Blood samples were drawn after an overnight fast into tubes containing EDTA, and plasma was immediately separated by low-speed centrifugation. HDL-containing fractions were obtained after precipitation of apolipoprotein B–containing lipoproteins by heparin-$MnCl_2$ at 4°C. Total cholesterol and triglycerides were determined using commercial kits (BioMérieux). LDL was calculated by the Friedewald formula, except for triglycerides >4 mmol/l; in that case, LDL was measured after ultracentrifugation. The plasma concentrations of apolipoprotein B were determined by radioimmunoassay. Non-HDL cholesterol was calculated using the following formula: total cholesterol − HDL. HbA_{1c} levels were determined by high-performance liquid chromatography. Microalbuminuria was assessed on a miction sample; when levels were >20 mg/l, a second determination of 24-h albumin urinary excretion was made. Microalbuminuria was defined as albumin excretion of 30–300 mg/day.

β-Blockers and calcium blockers were stopped 72 h before exercise testing. Exercise was stopped when patients were exhausted, if they developed angina or severe dyspnea, if the systolic blood pressure decreased by ≥15 mmHg, or if ventricular arrhythmia or ST depression >2 mm occurred. The exercise treadmill test (ETT) was considered positive when ≥1 mm ST-segment depression occurred at 80 ms after J point. ETT was considered negative when no ST depression occurred in a patient who achieved ≥85% of maximal age-predicted heart rate. Suboptimal ETT was defined as no ST depression with maximal heart rate achieved was <85% of predicted.

Patients with a suboptimal ETT underwent a single proton emission computed tomography protocol (in fasting state) using technetium-99m sestamibi, and stress testing was performed with dipyridamole. β-Blockers and calcium antagonists were stopped 72 h before the exploration. Images were visually interpreted using a semiquantitative color scale by two observers who performed the examination and were subsequently analyzed, in a blind fashion, by a third observer.

Ultrasonographic scanning of the carotid arteries was performed using high-resolution mode B ultrasound (Hitachi EUB 415F) with an electrical linear transducer (midfrequency, 7.5 MHz). Each measure was the mean of 16 determinations performed in plaque-free areas on the last centimeter of both primitive carotid arteries, as previously described (20). All the measurements were performed by the same experienced physician. The intraindividual variation coefficient was tested in two control groups: 6.55 ± 1.8% in 12 healthy subjects and 5.2 ± 0.7% in 10 diabetic patients.

Statistical analysis

Statistical analysis was performed by SSPS 11.0 software. Continuous variables were expressed as means ± SD and categorical variables as frequency and percent. Comparisons between groups (with and without cardiovascular events) were performed with one-way ANOVA for continuous variables and χ^2 test for categorical variables. A logistic regression analysis (with cardiovascular events as the outcome variable) was made to determine whether IMT was an independent predictor of cardiovascular events. Kaplan-Meier curves were generated to assess survival free of events and were compared using a log-rank test. The potential increment in prognostic value conferred by carotid IMT measurement was tested by two

Table 1—*Baseline characteristics of patients according to the occurrence of cardiovascular events*

	Cardiovascular events	No cardiovascular events	*P* value
n	34	195	
Sex (M/F)	25/9	123/72	0.24
Age (years)	58.9 ± 7.5	54.9 ± 7.8	0.007
Smokers	10 (29.4)	43 (22)	0.36
BMI (kg/m^2)	28.2 ± 3.7	28.8 ± 5.2	0.54
Hypertension	20 (58.8)	89 (45.6)	0.16
HbA_{1c} (%)	9.3 ± 1.8	8.9 ± 2.0	0.28
Total cholesterol (mmol/l)	2.04 ± 1.16	1.82 ± 1.21	0.33
HDL (mmol/l)	0.97 ± 0.28	1.06 ± 0.30	0.13
LDL (mmol/l)	3.70 ± 0.88	3.46 ± 0.93	0.15
Non-HDL cholesterol (mmol/l)	4.57 ± 0.99	4.25 ± 1.06	0.10
Antidiabetic agents	27 (79.4)	142 (72.8)	0.42
Metformin	4	29	0.70
Sulfonylureas	8	46	
Sulfonylureas and metformin	15	67	
Antihypertensive drugs	10 (29.4)	49 (25.1)	0.60
Hypolipidemic drugs	8 (23.5)	43 (22.0)	0.85
Fibrates	6	40	0.27
Statins	2	3	
Antiplatelet agents	3 (8.8)	12 (6.2)	0.56

Data are means ± SD or *n* (%).

ways: *1*) using a new categorical variable, a combined index, taking into account both carotid IMT and Framingham score (0 if carotid IMT and Framingham score are below median values, 1 if carotid IMT or Framingham score is above median value, or 2 if carotid IMT and Framingham score are above median values); and *2*) using a multivariate Cox regression analysis (coronary events as outcome variable). $P < 0.05$ was considered significant for all tests.

RESULTS

Cardiovascular events and cardiovascular risk predictors

As shown in Table 1, patients were mostly middle-aged men with elevated BMI, moderate hypertriglyceridemia, and low HDL concentration. Overall, 23% were current smokers, 48% had hypertension, and 24% had microalbuminuria. Glycemic control as assessed by HbA_{1c} was poor. The mean number of additional cardiovascular risk factors per patient was 2.6 ± 1.4. The mean ± SD of 10-year coronary risk according to Framingham score was 10.9 ± 8.4%. The exercise electrocardiogram was positive in only one patient and suboptimal for 13% of patients. In the subgroup of patients with suboptimal electrocardiograms, the freuency of abnormal myocardial scintigraphy was 25%. Carotid plaque was reported in 50% of patients. Carotid IMT was 0.84 ± 0.14 mm.

During the 5-year follow-up, 34 cardiovascular events, 28 coronary events, and 6 strokes were recorded, leading to 14.75 and 12.2% 5-year absolute cardiovascular and coronary risks, respectively. Patients who presented an event were older, had elevated carotid IMT, more cardiovascular risk factors, and higher Framingham scores than patients free from events (Tables 1 and 2). A suboptimal exercise electrocardiogram and the presence of carotid plaques were more frequent in the subgroup with cardiovascular events (Table 2). There was also a trend to an elevation of non-HDL cholesterol concentrations and of the proportion of microalbuminuric patients in the subgroup with cardiovascular events (Tables 1 and 2). There was no difference between groups concerning the type and frequency of hypoglycemic agents used (Table 1). The frequency of treatments aimed to reduce cardiovascular risk (hypolipidemic, antihypertensive, or antiplatelet drugs) was similar between groups (Table 1). In multivariate analysis using a model including age, carotid IMT, suboptimal electrocardiogram, microalbuminuria, and non-HDL cholesterol, carotid IMT was the only statistically significant independent predictor of cardiovascular events ($P = 0.045$) (Table 3). The odds ratio of cardiovascular risk for increase in 1 SD (0.13 mm) of carotid IMT was 1.63 (95% CI 1.01–2.63).

Incremental prediction for coronary events conferred by assessment of both carotid ultrasonography and Framingham coronary risk score

Kaplan-Meier curves showed a significant difference in survival free of coronary events between patients according to Framingham score (using the median of 10.5% as the cutoff value; log rank 9.1; $P = 0.0026$) (Fig. 1*A*) and carotid IMT (using the median of 0.835 mm as the cutoff value; 10.1; $P = 0.0015$) (Fig. 1*B*). The predictive value for coronary events was similar for carotid IMT and Framingham score as assessed by area under the receiver operating characteristic (ROC) curves (0.715 vs. 0.720, respectively).

Table 2—*Nontraditional cardiovascular risk markers according to the occurrence of cardiovascular events*

	Cardiovascular events	No cardiovascular events	*P* value
n	34	195	
Microalbuminuria	12 (35.3)	42 (21.5)	0.07
Suboptimal exercise electrocardiogram	8 (23.5)	21 (10.8)	0.04
Carotid IMT (mm)	0.92 ± 0.13	0.83 ± 0.13	0.0001
Carotid plaques	22 (64.7)	93 (47.7)	0.04
Number of cardiovascular risk factors	3.2 ± 1.4	2.5 ± 1.4	0.006
Framingham 10-year risk (%)	15.0 ± 7.8	10.2 ± 8.3	0.002

Data are means ± SD or *n* (%).

Table 3—*Logistic regression*

	Exp(B) (95% CI)	*P* value
Carotid IMT	1.63 (1.01–2.63)	0.045
Age	1.60 (0.81–3.16)	0.173
Suboptimal exercise	1.83 (0.59–5.72)	0.297
Microalbuminuria	1.88 (0.72–4.90)	0.196
Non-HDL cholesterol	1.23 (0.71–2.13)	0.463

Exp(B) corresponds to an increase of 1 SD.

Using the combined index as described above, the difference in survival shown by Kaplan-Meier curves is clearly increased (16.1, $P = 0.0003$) (Fig. 1*C*). The occurrence of a coronary event upon 5-year follow-up was observed in up to 24.2% of patients with a combined index value of 2 and in only 4.7% of patients with a combined index value of 0. The incremental value of carotid IMT was also assessed by developing a sequence of Cox models, starting with absolute number of cardiovascular risk factors, adding Framingham score (dichotomous variable above or below median value) and finally carotid IMT. The global χ^2 of the statistical model increased from 14.1 to 18.1 ($P = 0.035$) when carotid IMT was added as a continuous variable and from 12.7 to 16.6 ($P = 0.035$) when carotid IMT was expressed as a dichotomous variable (median value as cutoff point). Including the presence of carotid plaques instead of carotid IMT in the model was not associated with any increase in global χ^2.

CONCLUSIONS — Our prospective study has shown that carotid IMT was an independent predictor of incident cardiovascular events during the 5-year follow-up of middle-aged asymptomatic type 2 diabetic subjects. Previous studies reported that carotid IMT is a good indicator of the presence and extent of cardiovascular diseases in observational studies and that increased carotid IMT is associated with increased incidence of cardiovascular events in general and in diabetic populations (10,12–15,18). In our study, the odds ratio for cardiovascular events per SD increase in carotid IMT was 1.63 (95% CI 1.01–2.63), in accordance with results of other larger studies showing 1.43 (1.16–1.78) for myocardial infarction and 1.41 (1.25–1.82) for stroke in the Rotterdam Study, 1.92 (1.66–2.22) in women and 1.32 (1.13–1.54) in men for coronary heart disease in the Atherosclerosis Risk in Communities study, and 1.35 (1.25–1.45) for combined cardiovascular events in the Cardiovascular Health Study (12,13,15).

The original design of our study was to evaluate the incremental prediction of coronary events conferred by measurement of carotid IMT, in addition to a more conventional detection of silent myocardial ischemia and estimation of coronary risk by Framingham score. The sensibility of exercise treadmill test was poor in this middle-aged asymptomatic population due partly to many suboptimal workloads. Conversely, a suboptimal exercise test was more frequently observed in the group with subsequent cardiovascular events. It is in agreement with previous studies that reported low sensibility of exercise treadmill test in asymptomatic populations and worse cardiovascular prognosis in case of suboptimal test (3,9). The observed absolute coronary incidence for a 5-year follow-up was 12.2%, confirming that middle-aged French diabetic subjects have a high coronary risk over the traditional threshold of >2% per year.

The incidence of coronary events is similar for patients with carotid IMT above the median value and for patients with Framingham score above the median value. Accordingly, the areas under the ROC curves for carotid IMT and Framingham score are similar (0.715 and 0.720, respectively), in good agreement with data of the Rotterdam Study in general population (ROC areas 0.71 and 0.72 for carotid IMT and conventional cardiovascular risk factors, respectively) (21). The measurement of carotid IMT has a power to predict coronary events that is similar to Framingham score, but the association of these two indexes significantly improves the risk prediction, as shown by an increase in global χ^2 in Cox model. The

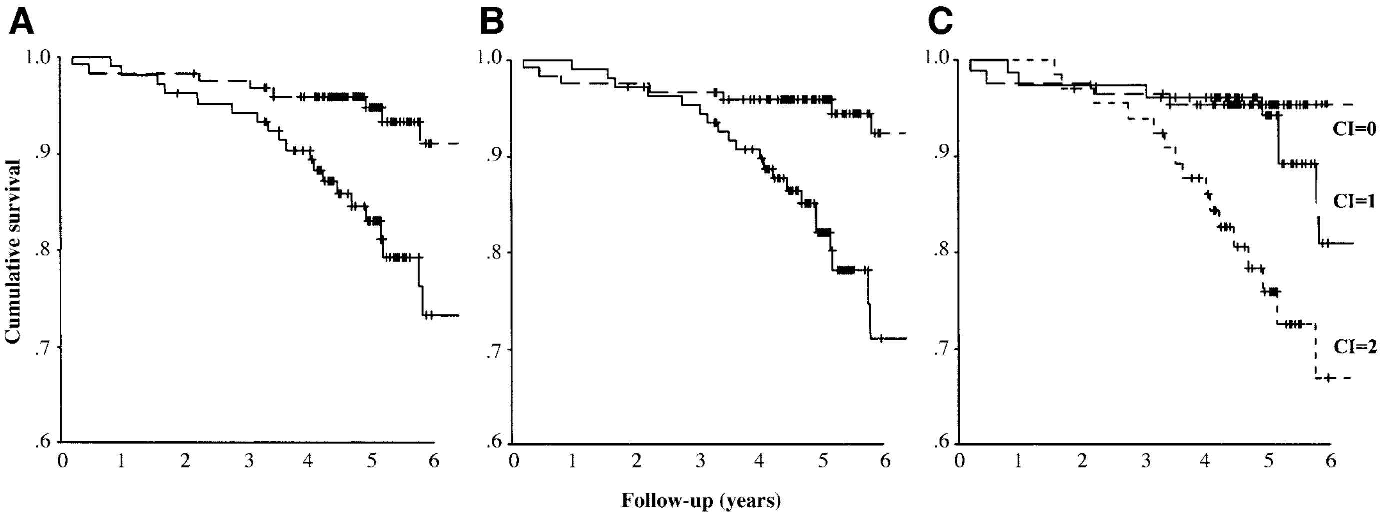

Figure 1—A: *Coronary event–free survival in patients according to Framingham score under (dotted line) or above (solid line) median value.* B: *Carotid IMT under (dotted line) or above (solid line) median value.* C: *Combined index value of 0, 1, or 2.*

combined use of carotid IMT and Framingham score may help to stratify the patients who need further screening tests for silent myocardial ischemia or who need an intensification of primary prevention. Because up to 24.2% of subjects with both carotid IMT and Framingham score above the median value will present future coronary events in the 5-year follow-up period, this subgroup of patients should be considered similar to subjects in secondary prevention, and intensive risk factor intervention can be efficiently focused on this very-high-risk population. Patients with a combined index of 1 (i.e., carotid IMT or Framingham score above the median values) will present future coronary events in 10.3%, and this subgroup with intermediate risk may be proposed to be screened with stress tests.

In conclusion, our study clearly shows that the use of an index related to the arterial wall such as carotid IMT is a contributive marker of cardiovascular risk in this type 2 diabetic cohort. It provides a predictive value for occurrence of coronary events similar to that observed for Framingham score. Moreover, the combination of these two indexes significantly improves coronary risk prediction and consequently may contribute substantially for efficient patient management.

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