Cardiovascular Risk Prediction Is Improved by Adding Asymptomatic Coronary Status to Routine Risk Assessment in Type 2 Diabetic Patients

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OBJECTIVE—To evaluate if silent myocardial ischemia (SMI) and silent coronary artery disease (CAD) provide significant additional value to routine cardiovascular risk assessment in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS—We followed up to a first cardiovascular event 688 subjects (322 men, aged 59 ± 8 years) out of 731 consecutive asymptomatic type 2 diabetic patients with ≥1 additional risk factor who had been prospectively screened between 1992 and 2006 for SMI by stress myocardial scintigraphy and for silent CAD by coronary angiography.

RESULTS—SMI was found in 207 (30.1%) patients and CAD in 76 of those with SMI. Of the patients, 98 had a first cardiovascular event during a 5.4 ± 3.5 (range: 0.1–19.2) year follow-up period. Cox regression analysis considering parameters predicting events but not SMI and CAD ("routine assessment") showed in univariate analyses that macroproteinuria (hazard ratio [HR] 3.33 [95% CI 1.74–6.35]; $P < 0.001$), current multifactorial care (0.27 [0.15–0.47]; $P < 0.001$), and peripheral/carotid occlusive arterial disease (PCOAD; 4.33 [2.15–8.71]; $P < 0.001$) independently predicted cardiovascular events. When added into the model, SMI (HR 1.76 [1.00–3.12]; $P = 0.05$) and CAD (2.28 [1.24–4.57]; $P < 0.01$) were also independently associated with events. SMI added to the prediction of an event in the following 5 years above and beyond routine assessment risk prediction (c statistic with or without SMI 0.788 [0.720–0.855] and 0.705 [0.616–0.794], respectively).

CONCLUSIONS—Although screening for SMI and silent CAD should not be systematic, these complications are predictive of cardiovascular events in type 2 diabetic patients in addition to routine risk predictors, especially represented by PCOAD, macroproteinuria, and nonintensive management.

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Type 2 diabetes is associated with a high prevalence of coronary artery disease (CAD) and cardiovascular events (1,2). Other cardiovascular risk factors are common in this population and must be taken into account for the estimation of the cardiovascular risk, such as in the United Kingdom Prospective Diabetes Study (UKPDS) risk engine (3) or the Framingham equation (4). However, since these models have been created, cardiovascular risk factors have been better controlled in accordance with guidelines. Therefore, the performances of these models have recently been discussed (5,6). It has been suggested that markers of subclinical organ damage (7) and some specific markers, such as nephropathy (8) or retinopathy (9), could be considered for cardiovascular risk stratification.

Silent myocardial ischemia (SMI) is two- to fourfold more frequent in type 2 diabetic patients as compared with the nondiabetic population (1,2). SMI has been reported in 10–65% of the diabetic population (10) and is a strong predictor for incident coronary events and premature death (11,12), especially when it is associated with silent CAD (i.e., angiography-diagnosed coronary stenoses) (13). We raised the hypothesis that the prognostic value of SMI and silent CAD was better than routine cardiovascular risk assessment. Therefore, the aim of the current study was to evaluate if ischemic and coronary status (SMI and silent CAD) provided significant additional value to routine cardiovascular risk assessment in asymptomatic type 2 diabetic patients with at least one other cardiovascular risk factor.

RESEARCH DESIGN AND METHODS

The patients were prospectively recruited in the Diabetes Department of Jean Verdier Hospital between 1992 and 2006. This study was approved by the ethical committee of Reims, France. Each patient gave informed consent for enrollment in accordance with the European directives. Eligibility criteria included type 2 diabetes; no history of myocardial infarction or angina pectoris; normal 12-lead resting electrocardiogram (ECG); and presence of at least one of the following additional cardiovascular risk factors: dyslipidemia, hypertension, smoking, nephropathy, family history of premature CAD, and peripheral/carotid occlusive arterial disease (PCOAD) (14). Exclusion criteria included congenital heart disease or known cardiomyopathy. Diabetic retinopathy was graded according to the Early Treatment of Diabetic Retinopathy Study severity scale and defined as absent or present, and also as absent, mild/moderate (minimal and moderate nonproliferative retinopathy), and severe (severe nonproliferative or proliferative retinopathy). The diagnosis of peripheral neuropathy was based on the presence of any two or more of the following: neuropathic symptoms,

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decreased distal sensation, or decreased or absent ankle reflexes. Data on the treatments used during the follow-up were not available. Because antidiabetic, lipid-lowering, and antihypertensive treatments have been more intensively used since the year 2000 (15), we considered the percentage of follow-up time spent after 2000 to estimate the quality of treatment. When the follow-up duration spent after year 2000 was ≥10% of the overall follow-up duration, the patient was considered as being on current multifactorial care. Finally, the 10-year cardiovascular UKPDS (3) and the 10-year cardiac Framingham (4) risk scores were calculated.

Cardiovascular investigations

The protocol was previously reported (10,13,14). Each patient underwent a ^{201}Tl myocardial scintigraphy after an ECG stress test, a pharmacological stress test (dipyridamole injection), or both. The ECG stress test was performed in patients who could exercise on a bicycle ergometer and were expected to have an interpretable exercise ECG. When the patient was unable to exercise or when the ECG stress test result was indeterminate, a pharmacological stress test using dipyridamole was carried out. SMI was defined as an abnormal ECG stress test, an abnormal myocardial scintigraphy imaging (i.e., defects in at least 3 out of 17 segmental regions), or both. A selective coronary angiography was performed in the patients with SMI within a period of 2 months after the noninvasive investigation. CAD was defined either as a ≥70% narrowing of the luminal diameter in the left anterior descending artery, the circumflex artery, a well-developed marginal vessel, or the right coronary artery or as a ≥50% narrowing of the left main coronary artery diameter.

Biological measurements

The following measurements were recorded at the time of screening for SMI: HbA_{1c} (Dimension technology, Siemens Healthcare Diagnosis Inc., Newark, NJ), serum total cholesterol, HDL cholesterol and triglycerides (enzymatic colorimetry, Hitachi 912, Roche Diagnostics, Meylan, France), creatininemia (colorimetry, Kone Optima, Thermolab System, Paris La Défense, France), 24-h proteinuria, and the 24-h urinary albumin excretion rate (laser immunonephelometry, BN100, Dade-Behring, Paris, France). LDL cholesterol was calculated according to the Friedewald formula and creatinine clearance with the Cockcroft formula.

Follow-up

The date of the noninvasive cardiac testing was considered to be the beginning of the follow-up. The follow-up procedure included cardiovascular examination at least once a year. The patients were evaluated for cardiovascular signs and symptoms (angina, dyspnea, edema, and arrhythmia) and had a 12-lead ECG. For each cardiac event, medical records were obtained from the hospital or the primary care physician. When a patient died, the cause of death was documented with the help of the family, the general practitioner, or the cardiologist. The following cardiovascular events were considered: death of cardiac origin (sudden death, death caused by myocardial infarction, or congestive heart failure), nonfatal acute coronary syndrome, heart failure (New York Heart Association stage III or IV and need for hospitalization), secondary need for coronary revascularization, lower limb or carotid revascularization procedure, lower leg amputation, and stroke. The follow-up was stopped when the first event occurred.

Statistical analysis

Continuous variables were expressed as means ± SD values and compared by one-way ANOVA or Mann-Whitney *U* test as adequate. The significance of differences in proportions was tested with the χ^2 test. Because great interindividual differences were observed in the duration of follow-up, two types of analyses were conducted.

In the first analysis, the Kaplan-Meier method was used to examine the time-dependent cumulative probabilities of cardiovascular events. Cox regression analyses were used to determine hazard ratios (HRs) for cardiovascular events in relation to the parameters that predicted cardiovascular events according to the Kaplan-Meier method. We considered the cumulative probabilities of cardiovascular events first according to the presence of SMI or CAD after adjustment on the parameters included in the Cox regression analyses and then according to subgroups, considering routine cardiovascular risk assessment and the presence of SMI or CAD.

In the second analysis, we limited the statistical analysis to a 5-year follow-up. Logistic regression was used for multivariate analyses based on models including the factors that were associated with the occurrence of a cardiovascular event during the first 5 years of follow-up with a *P* value ≤ 0.10 in univariate analyses. We used c statistic to determine if SMI or CAD added to the prediction of a cardiovascular event above and beyond the risk prediction based on the other parameters. Finally, we calculated the Hosmer-Lemeshow χ^2 statistic (HLχ^2) to test the difference in expected and observed probabilities of an event in the different models.

Statistical analyses were carried out using SPSS software (SPSS, Chicago, IL). The 0.05 probability level was considered for statistical significance.

RESULTS

Patients' characteristics

A total of 731 patients were enrolled between 1992 and 2006. Among them, 688 were followed, whereas 43 (6.0%) were lost to follow-up. The latter patients did not differ significantly from the former when considering either the main clinical and biological criteria or the SMI status (data not shown). The main baseline characteristics of the 688 patients are described in Table 1. SMI was diagnosed in 207 of them (30.1%). A coronary angiography was subsequently performed in 191 of the 207 subjects with SMI. Out of them, 76 (i.e., 11.0% of the 688 patients) had CAD, including one-vessel disease in 47 and two- and three-vessel disease in 15 and 14 patients, respectively.

Follow-up

Of the 76 patients with silent CAD, 22 were treated by coronary angioplasty and 6 by coronary artery bypass, whereas the remaining patients were medically treated, according to the cardiologist's decision. These initial revascularization procedures were not counted as cardiovascular events. A total of 98 patients had a first cardiovascular event during a 5.4 ± 3.5 (range: 0.1–19.2) year period: 10 cardiac deaths, 39 acute coronary syndromes, 10 nonfatal congestive heart failures, 1 secondary coronary revascularization procedure, 21 strokes, 12 peripheral revascularization procedures, and 5 lower-leg amputations.

Kaplan-Meier survival analyses showed that SMI (adjusted log-rank test 21.2, $P < 0.0001$), the presence of both SMI and silent CAD (log rank 47.2, $P < 0.0001$), retinopathy whatever its stage (log rank 11.7, $P < 0.001$), severe retinopathy (log rank 5.8, $P < 0.05$), diabetic nephropathy (log rank 5.1, $P = 0.025$), macroproteinuria (log rank 16.0, $P < 0.001$), PCOAD

Table 1—*Characteristics of the total population of the 688 patients who were followed up and of the patients who did or did not have a 5-year occurrence of a first cardiovascular event* (n = 371)

	Total (n = 688)	Patients without a 5-year event (n = 306)	Patients with a 5-year event (n = 65)	Odds ratio (95% CI)	P value
Clinical characteristics					
Age (years)	58.9 ± 8.5	57.9 ± 8.2	60.6 ± 8.5		<0.05
Age ≥70 years (%)	84 (12.2)	23 (7.5)	16 (24.6)	4.02 (1.98–8.14)	<0.001
Sex (Men/Women)	322/366	151/155	40/25		0.077
BMI (kg/m^2)	30.1 ± 6.1	29.2 ± 5.3	30.0 ± 5.6		NS
Diabetes					
Duration (years)	12.9 ± 7.6	12.4 ± 6.9	15.2 ± 8.3		<0.01
Duration >20 years (%)	111 (16.1)	39 (12.7)	16 (24.6)	2.24 (1.16–4.31)	<0.05
HbA_{1c} (%)	8.9 ± 2.2	9.1 ± 2.4	9.5 ± 2.1		NS
HbA_{1c} ≥10% (%)	196 (29.6)	94 (31.9)	28 (45.9)	1.81 (1.04–3.18)	<0.05
Retinopathy (%)	232 (34.3)	95 (31.6)	30 (46.9)	1.91 (1.11–3.31)	<0.05
Severe retinopathy (%)	54 (8.0)	20 (6.6)	8 (12.5)		NS
Nephropathy (%)	240 (34.9)	91 (29.7)	30 (46.2)	2.03 (1.17–3.50)	<0.05
Macroproteinuria (%)	59 (9.5)	12 (4.3)	11 (19.6)	5.40 (2.25–12.98)	<0.0001
Peripheral neuropathy (%)	317 (46.6)	134 (44.1)	38 (59.4)	1.85 (1.07–3.21)	<0.05
Cardiovascular risk factors					
Hypertension (%)	463 (70.7)	196 (68.8)	47 (74.6)		NS
Dyslipidemia (%)	418 (64.4)	176 (61.5)	39 (67.2)		NS
Smoking (%)	147 (21.5)	66 (21.6)	21 (32.3)		0.076
≥2 Cardiovascular risk factors (%)	407 (66.6)	163 (59.5)	41 (69.5)		NS
Framingham risk score (%)	20.2 ± 10.9	19.7 ± 11.1	24.9 ± 11.4		<0.01
Framingham risk score ≥20% (%)	254 (45.9)	103 (43.1)	35 (67.3)	2.72 (1.44–5.12)	<0.01
UKPDS risk score (%)	26.9 ± 17.5	26.2 ± 18.4	33.2 ± 16.7		<0.05
UKPDS risk score ≥20% (%)	331 (58.0)	141 (56.4)	37 (71.2)		0.062
Follow-up spent after 2000 (%)	64.9 ± 40.5	51.4 ± 45.2	48.9 ± 48.3		NS
Cardiovascular status					
PCOAD (%)	58 (8.4)	8 (2.6)	16 (24.6)	6.81 (3.13–14.8)	<0.0001
SMI (%)	207 (30.1)	86 (28.1)	38 (58.5)	3.60 (2.07–6.23)	<0.0001
Silent CAD (%)	76 (11.3)	24 (8.0)	25 (38.5)	7.21 (3.76–13.8)	<0.0001

Data are n (%) or mean ± SD. NS, not significant.

(log rank 56.6, $P < 0.001$), a Framingham risk score ≥20% (log rank 7.6, $P < 0.01$), a UKPDS risk score ≥20% (log rank 8.0, $P < 0.01$), and current multifactorial care (protective, log rank 83.3, $P < 0.0001$) were significant predictors of cardiovascular events. Three models of Cox regression analyses were built (Table 2). The routine variables that predicted cardiovascular events, including Framingham or UKPDS risk score, were entered into model 1. SMI (model 2) or CAD (model 3) was then added to model 1. In model 1, macroproteinuria, current multifactorial care, and PCOAD were independently predictive of cardiovascular events (model 1 with UKPDS risk score: χ^2 65.5; model 1 with Framingham risk score: χ^2 61.1). SMI in model 2 was additionally and independently predictive of cardiovascular events (χ^2 69.0 with UKPDS risk score and 64.5 with Framingham risk score) as CAD was in model 3 (χ^2 73.5 with UKPDS risk score and 71.0 with Framingham risk score). The cumulative probabilities of cardiovascular event according to the presence of SMI or CAD after adjustment on the parameters from model 1 (with UKPDS risk score) are shown in Fig. 1*A* and *B*. This figure also shows that the cumulative probability of cardiovascular events increased with the presence of at least one of the following criteria: macroproteinuria, no current multifactorial care, and PCOAD or with SMI (Fig. 1*C*), CAD (Fig. 1*D*), or both.

Table 1 shows the variables that were associated with the occurrence of a cardiovascular event during the first 5 years of follow-up. The variables predicting cardiovascular events were entered into three logistic regressions: UKPDS risk score ≥20% (age, sex, smoking, diabetes duration >20 years, and HbA_{1c} ≥10% were not entered into the model because they were already included in this score), retinopathy, nephropathy, peripheral neuropathy, and PCOAD in model a; plus SMI in model b; and plus CAD in model c. The results are shown in Table 3; macroproteinuria, PCOAD (model a, b, and c), and SMI (model b) or CAD (model c) were independently predictive of a cardiovascular event during the first 5 years. The area under the receiver operating characteristic (AROC) curve for model a parameters to predict a 5-year cardiovascular event was 0.705 (95% CI 0.616–0.794; $P < 0.001$). When the presence of SMI (model b) or CAD (model c) was added into the model, the AROC curve increased to 0.788 (0.720–0.855; $P < 0.0001$) or 0.779 (0.701–0.857; $P < 0.001$), respectively. HLχ^2 were 1.34, P = 0.932; 5.13, P = 0.643; and 1.77, P = 0.940 for models a, b, and c, respectively.

The same statistic was built using the Framingham risk score ≥20% (but not age, sex, or smoking, which were already included in this score), diabetes duration >20 years, HbA_{1c} ≥10%, retinopathy, macroproteinuria, peripheral neuropathy,

Table 2—*HRs for cardiovascular events for parameters associated with events in Kaplan-Meier analyses (multiple Cox regression models)*

UKPDS	HR (95% CI)	*P* value	Framingham	HR (95% CI)	*P* value
Model 1: Routine assessment					
χ^2 65.5			χ^2 61.1		
Risk score ≥20%		NS	Risk score ≥20%		NS
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.6 (1.9–6.9)	<0.001	Macroproteinuria	3.3 (1.7–6.3)	<0.001
Current multifactorial care	0.28 (0.15–0.50)	<0.001	Current multifactorial care	0.27 (0.15–0.47)	<0.001
PCOAD	4.9 (2.5–9.8)	<0.001	PCOAD	4.3 (2.1–8.7)	<0.001
Model 2: Routine + SMI assessment					
χ^2 69.0			χ^2 64.5		
Risk score ≥20%		NS	Risk score ≥20%		NS
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.0 (1.6–5.9)	<0.01	Macroproteinuria	2.8 (1.4–5.5)	<0.01
Current multifactorial care	0.26 (0.14–0.45)	<0.001	Current multifactorial care	0.25 (0.14–0.45)	<0.001
PCOAD	4.4 (2.2–8.7)	<0.001	PCOAD	3.8 (1.9–7.7)	<0.001
SMI	1.8 (1.0–3.2)	0.05	SMI	1.8 (1.0–3.1)	0.05
Model 3: Routine + CAD assessment					
χ^2 73.5			χ^2 71.0		
Risk score ≥20%		NS	Risk score ≥20%		NS
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.4 (1.7–6.6)	<0.001	Macroproteinuria	2.9 (1.5–5.7)	<0.01
Current multifactorial care	0.29 (0.16–0.53)	<0.001	Current multifactorial care	0.27 (0.16–0.50)	<0.0001
PCOAD	4.5 (2.3–9.1)	<0.001	PCOAD	4.0 (1.9–8.0)	<0.0001
Silent CAD	2.1 (1.1–4.1)	<0.05	Silent CAD	2.3 (1.2–4.6)	<0.01

A follow-up spent after year 2000 <10% is considered as current multifactorial care. NS, not significant.

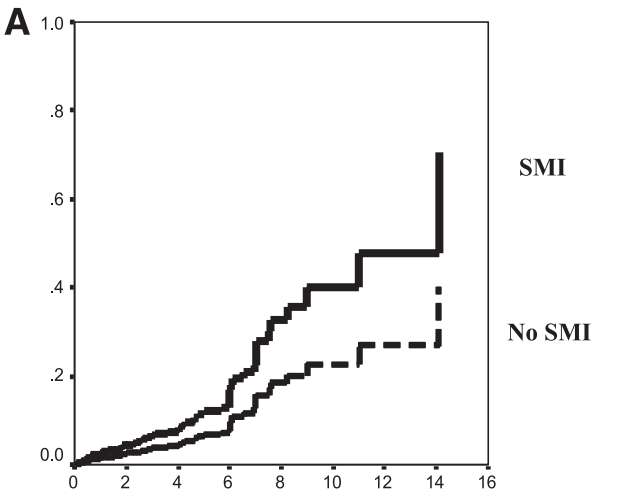
and PCOAD in model a; plus SMI in model b; and plus CAD in model c. Framingham risk score and PCOAD (model a, b, and c), HbA_{1c} and macroproteinuria (model a), and SMI (model b) or CAD (model c) were independently predictive of 5-year events (Table 3).

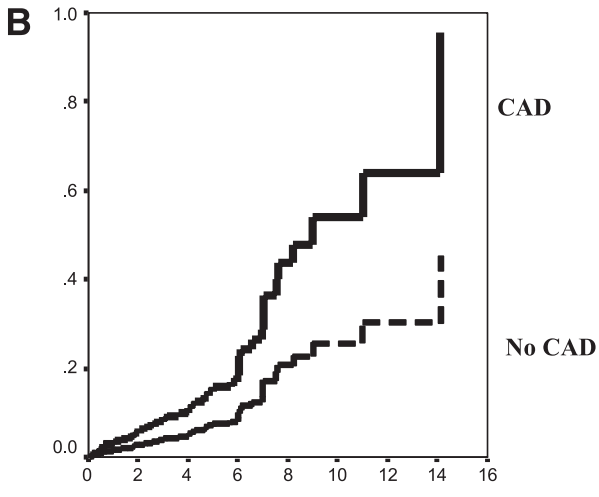
CONCLUSIONS—The present data show that in this cohort of asymptomatic type 2 diabetic patients with at least one additional cardiovascular risk factor, the performances of UKPDS or Framingham risk scores to predict cardiovascular events are limited and may be improved by considering the presence of macroproteinuria and PCOAD. Furthermore, we show here for the first time that the presence of SMI or silent CAD is independently associated with cardiovascular events and improves cardiovascular risk prediction.

Although some studies (16) suggest that the presence of diabetes should be regarded as a risk of coronary mortality similar to established CAD, we show in the current study that type 2 diabetic patients may be further stratified by evaluating their a priori cardiovascular risk using the calculation of a specific (UKPDS) or nonspecific (Framingham) risk score. However, the association between a high risk score and the occurrence of events disappeared in multivariate analyses (Table 2). Recent studies have also shown that risk equations are likely to overestimate cardiovascular risk (5,6), partly because the current multifactorial therapy has markedly improved the cardiovascular prognosis in the diabetic population. In the current study, we considered the year 2000 as the threshold time, from when the treatment of risk factors has been intensified in accordance to the current guidelines (15). It is interesting that shorter time exposure to contemporary treatment (expressed as percentage of follow-up duration spent after 2000) was independently predictive of events.

Other parameters may be useful to evaluate the cardiovascular prognosis in the diabetic population, such as the presence of retinopathy or nephropathy. The presence of these microangiopathic complications has usually been considered as a good marker of exposure (in time and intensity) not only to hyperglycemia but also to other risk factors including hypertension. In the current study, any stage of retinopathy and severe retinopathy both predicted events, although only severe retinopathy was previously shown to be associated with a high cardiovascular risk (9). Our data also support the high risk of events associated with incipient nephropathy and the even higher risk associated with macroproteinuria (8).

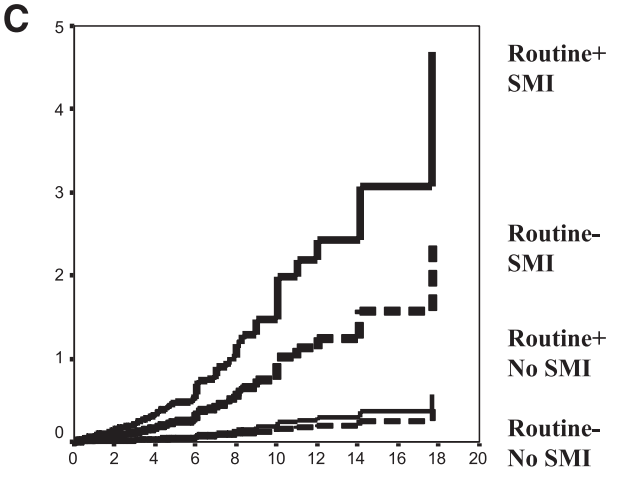
An alternative could be the identification of vascular integrators of risk (i.e., parameters that may reflect the cumulative exposure to cardiovascular risk factors and its intensity). For example, it was shown that the presence of arterial stiffness or arteriosclerotic plaques could improve the risk prediction when added to the Systemic Coronary Risk Evaluation in healthy subjects (17). In the current study, PCOAD was an independent predictor of cardiovascular events. The procedure for diagnosing PCOAD is usually easy, with ultrasound examination being performed especially in patients with clinical signs or symptoms. Screening for SMI and subsequently silent CAD is more complicated and expensive. Silent CAD in diabetic patients was shown to be associated with a higher incidence of cardiac events (10,11). With regard to diabetic patients with SMI but no CAD, we have previously reported evidence for abnormalities of coronary flow reserve and endothelium function and shown that such functional abnormalities were also associated with a worse prognosis (18). The current study confirms that both SMI

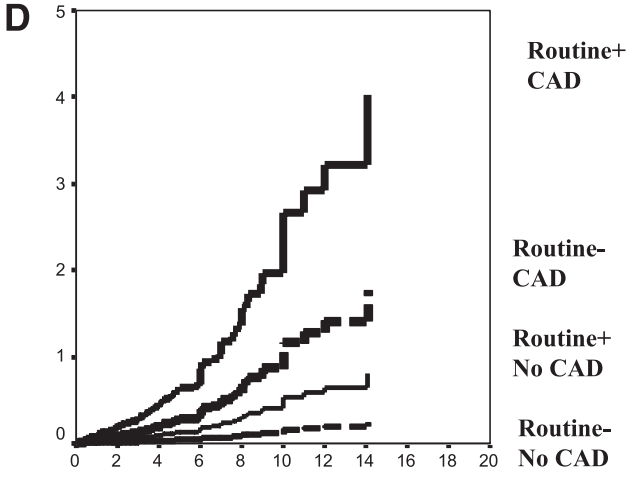




Adjusted model*	Hazard ratio [95CI]
No SMI	1
SMI	1.8 [1.0-3.2]

Adjusted model*	Hazard ratio [95CI]
No CAD	1
CAD	2.1 [1.1-4.1]





Model	Hazard ratio [95CI]
Routine-, no SMI	1
Routine+, no SMI	1.4 [0.6-3.5]
Routine-, SMI	6.2 [3.3-11.7]
Routine+, SMI	12.1 [6.4-22.5]

Model	Hazard ratio [95CI]
Routine-, no CAD	1
Routine+, no CAD	3.4 [1.2-9.2]
Routine-, CAD	7.3 [4.1-12.8]
Routine+, CAD	16.6 [8.6-32.2]

Figure 1—*Cumulative probability (%) and HRs of cardiovascular events according to SMI* (A) *and silent CAD* (B) *status and subgroups according to routine risk assessment and SMI* (C) *or silent CAD* (D). **After adjustment on macroproteinuria, current multifactorial care, PCOAD, UKPDS risk score >20%, and retinopathy. Routine assessment was based on the presence of at least one of the following criteria: macroproteinuria, no current multifactorial care, and PCOAD.*

and CAD are strong predictors of cardiovascular events and shows for the first time that diagnosing CAD in asymptomatic patients improves cardiovascular prediction in addition to the risk estimation based on traditional risk factors, risk equations, nephropathy, PCOAD, and current multifactorial care.

The present results are in line with some recommendations for SMI screening in diabetic patients with high cardiovascular risk (1,2,19). This proposal is, however, under debate (20,21) because of several considerations. First, such a screening cannot be performed in all diabetic patients,

Table 3—*Odds ratio for the 5-year occurrence of cardiovascular events for parameters associated with events in univariate analyses (logistic regression models)*

UKPDS	Odds ratio (95% CI)	*P* value	Framingham	Odds ratio (95% CI)	*P* value
Model a: Routine assessment					
AROC 0.705 (0.616–0.794)			AROC 0.762 (0.686–0.837)		
HLχ^2 1.34, *P* = 0.932			HLχ^2 6.62, *P* = 0.578		
Risk score ≥20%		NS	Risk score ≥20%	2.8 (1.3–5.9)	<0.01
			Diabetes duration >20 years		NS
			HbA_{1c} ≥10%	2.1 (1.0–4.2)	<0.05
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.9 (1.4–10.8)	<0.01	Macroproteinuria	3.2 (1.1–9.1)	<0.05
Peripheral neuropathy		NS	Peripheral neuropathy		NS
PCOAD	4.3 (1.6–11.3)	<0.01	PCOAD	4.7 (1.7–12.8)	<0.01
Model b: Routine + SMI assessment					
AROC 0.788 (0.720–0.855)			AROC 0.809 (0.744–0.875)		
HLχ^2 5.13, *P* = 0.643			HLχ^2 9.83, *P* = 0.277		
Risk score ≥20%		NS	Risk score ≥20%	2.6 (1.2–5.5)	<0.05
			Diabetes duration >20 years		NS
			HbA_{1c} ≥10%		NS
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.2 (1.1–9.2)	<0.05	Macroproteinuria		NS
Peripheral neuropathy		NS	Peripheral neuropathy		NS
PCOAD	4.0 (1.5–10.9)	<0.01	PCOAD	4.2 (1.5–12.0)	<0.01
SMI	3.2 (1.6–6.4)	<0.01	SMI	2.9 (1.4–6.1)	<0.01
Model c: Routine + silent CAD assessment					
AROC 0.779 (0.701–0.857)			AROC 0.817 (0.745–0.888)		
HLχ^2 1.77, *P* = 0.940			HLχ^2 5.37, *P* = 0.615		
Risk score ≥20%		NS	Risk score ≥20%	2.6 (1.2–5.7)	<0.05
			Diabetes duration >20 years		NS
			HbA_{1c} ≥10%		NS
Retinopathy		NS	Retinopathy		NS
Macroproteinuria	3.7 (1.3–11.0)	<0.05	Macroproteinuria		NS
Peripheral neuropathy		NS	Peripheral neuropathy		NS
PCOAD	4.0 (1.4–11.3)	<0.01	PCOAD	4.1 (1.4–12.0)	<0.01
Silent CAD	5.4 (2.4–12.2)	<0.001	Silent CAD	5.2 (2.2–12.1)	<0.001

NS, not significant.

and the current selection criteria still need to be improved (22,23). Second, the cardiovascular prognosis has been markedly improved in diabetic patients by intensifying preventive medical treatments. However, the current article shows that the prognosis associated with SMI remains poor despite more intensive treatment as prescribed since 2000. Finally, the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study has recently shown that screening for SMI was not associated with a better prognosis (12). However, very few patients with SMI underwent coronary angiography and revascularization during this study. Nevertheless, another randomized study suggested that screening for SMI and CAD may improve the prognosis if a coronary revascularization was performed in patients with coronary stenoses (24).

Our hospital-based study has some limitations. The diabetic patients who were included had at least one additional risk factor and, therefore, the results are not necessarily generalizable to the diabetic population. CAD status was unknown in the patients without SMI because they did not undergo a coronary angiography for ethical reasons. However, the present series includes the largest series ever published in the literature of coronary angiographies in patients with SMI. The number of cardiovascular events was limited. The prognosis was not adjusted on medical therapy but on the period of treatment.

In conclusion, SMI is a common condition in patients with type 2 diabetes and at least one additional cardiovascular risk factor. SMI and silent CAD are strong predictors of cardiovascular events in diabetic patients, beyond their a priori cardiovascular risk and independent of more or less intensive medical therapy. Risk prediction is improved by adding coronary status to routine prognosis assessment. However, screening for silent coronary disease is expensive and not easily available in routine assessment and, therefore, should not be performed in all diabetic patients. The selection criteria for screening still need to be improved, and the benefit of screening and subsequently treating SMI and silent CAD remains to be extensively addressed in further studies (25).

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