

Predictive Value of Silent Myocardial Ischemia for Cardiac Events in Diabetic Patients

Influence of age in a French multicenter study

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OBJECTIVE — Silent myocardial ischemia (SMI) in asymptomatic subjects with no history of myocardial infarction or angina is a frequent condition in diabetic patients. The aim of the study was to examine the predictive value of SMI for cardiac events in a multicenter cohort and to determine whether this value is higher in patients with a particular clinical profile.

RESEARCH DESIGN AND METHODS — A total of 370 asymptomatic diabetic patients with at least two additional cardiovascular risk factors was recruited in four departments of diabetology. SMI was assessed by either exercise or dipyridamole single-photon emission-computed tomography myocardial perfusion imaging with thallium-201. If dipyridamole stress was used, an electrocardiogram stress test was performed separately on another day. Follow-up duration was 3–89 months (38 ± 23 months).

RESULTS — There was evidence of SMI in 131 patients (35.4%) on at least one positive noninvasive test. The patients with SMI were significantly older and had significantly higher serum triglycerides and lower HDL cholesterol levels. Cardiac events occurred in 53 patients (14.3%). Major cardiac events (death or myocardial infarction) occurred in 38 patients (10%) and other events (unstable angina, heart failure, or coronary revascularization) occurred in 15 patients. The patients who had cardiac events were older and had higher serum triglyceride levels at baseline. There was a significant association between SMI and cardiac events (hazard ratio 2.79 [95% CI 1.54–5.04]) and in particular major cardiac events (3 [1.53–5.87]). In the patients >60 years of age, the prevalence of SMI was higher (43.4 vs. 30.2% in those <60 years). SMI was associated with a significant risk of cardiac events (2.89 [1.31–6.39]) and in particular major cardiac events (3.66 [1.36–9.87]) for the patients >60 years old but not for those <60 years old.

CONCLUSIONS — In asymptomatic diabetic patients with additional cardiovascular risk factors, SMI is a potent predictor of cardiac events and should be assessed preferably in the patients >60 years of age.

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Abbreviations: CAN, cardiac autonomic neuropathy; ECG, electrocardiogram; SMI, silent myocardial ischemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The prognostic value of type 1 silent myocardial ischemia (SMI) according to the Cohn classification, i.e., myocardial ischemia in asymptomatic subjects with no history of myocardial infarction or angina (1), has been evaluated in several studies in the general population. One of them had included 2,014 asymptomatic men whose mean age was 50 years and showed that within 13 years of follow-up, the rate of major cardiac events was four to five times higher in the patients with a positive exercise electrocardiogram (ECG) test than in those with a normal ECG stress test (2). Other studies have shown that a positive exercise ECG test predicts a 3–14 times higher rate of major cardiac events (3,4). Silent ischemic episodes during 24-h ECG monitoring have also been shown to be associated with a higher rate of major cardiac events in patients who suffer from unstable angina, myocardial infarction, or ECG ischemic changes at low levels of exercise (5) but not in patients with a stable coronary heart disease (6).

Regarding diabetic patients, type 1 SMI has been found in up to 35% of those without cardiac symptoms or signs but with other cardiovascular risk factors (7–12). In diabetic patients, only a few studies have evaluated the prognostic value of SMI, suggesting that SMI was associated with an increased rate of major cardiac events (11,13–16).

The aim of the present study was to examine the predictive value of type 1 SMI in a multicenter cohort of diabetic patients and to determine whether this value was higher in patients with a particular clinical profile.

RESEARCH DESIGN AND METHODS

Diabetic patients were consecutively recruited between 1991 and 1996 in four French departments of diabetology for the assessment of SMI. They gave their informed consent to participate in the study. This study was approved by the local ethics committees. All the patients fulfilled the following criteria

at inclusion: absence of myocardial infarction or angina, normal standard 12-lead ECG at rest, and diabetes duration >15 years for type 1 patients and >5 years for type 2 patients. The patients also met at least two of the following additional cardiovascular risk factors: either dyslipidemia (total cholesterol >6.5 mmol/l and/or triglycerides >2.5 mmol/l) or a lipid-lowering treatment, hypertension (blood pressure >140–90 mmHg or treatment with an antihypertensive drug), smoking, lower limb obstructive arterial disease, nephropathy defined by albuminuria >30 mg/day, or a family history of coronary artery disease before the age of 60. None of the patients had valvular heart disease, congenital heart disease or cardiomyopathy, asthma or severe chronic bronchopathy, end-stage renal failure (plasma creatinine >250 μ mol/l), thyroid disease, chronic alcohol consumption (>30 g/day), or morbid obesity (with BMI >40 kg/m²).

Initial cardiac assessment

Depending on the center, the protocol design for assessing SMI consisted of a thallium-201 myocardial scintigraphy performed either in conjunction with exercise testing or when performed with dipyridamole vasodilation followed by additional ECG stress testing on another day. The tests were done after discontinuation of drugs with potential antianginal effects (β -blockers and calcium channel blockers) for 2 days, according to a standard protocol.

The ECG stress test was performed in the same way, whether it was carried out separately or during the myocardial scintigraphy. When performed separately, it was monitored by the same investigator in each center. Similarly, myocardial scintigraphy was performed by a single investigator in each center. Briefly, the ECG stress test consisted of a graded exercise test on an ergometer bicycle, starting at a workload of 30 W and increasing by 30 W every 3 min to achieve \geq 85% of the maximum age-predicted heart rate. The test was considered positive if \geq 1 mm flat or downsloping ST-segment occurred at 0.08 s after the J point with or without angina pectoris.

Pharmacologic vasodilator stress was performed by the IV infusion of 0.56 mg/kg of dipyridamole over 4 min. Three or four millicuries of thallium-201 were injected after the completion of the dipyridamole infusion. Single-photon emission-computed tomography myocardial

perfusion imaging was started at 5–10 min after thallium-201 injection.

Three hours after the stress test, one mCi of thallium-201 was injected at rest, 15 min later (reinjection imaging). Images were acquired using a 180° circular orbit (32 projections), and transaxial sections were obtained and reoriented according to the three standard cardiac planes. The left ventricle was divided into 17 segments, and single-photon emission-computed tomography images were visually analyzed by two experienced observers blinded from clinical data, with consensus in case of disagreement. Each segment was classified as normal or abnormal and if abnormal, as a reversible or fixed defect. Myocardial perfusion imaging was defined as abnormal when a fixed or reversible perfusion defect involving at least two segments of the left ventricle was present.

Patients with abnormal myocardial perfusion imaging or a positive stress ECG during exercise or dipyridamole infusion or both were considered to have significant SMI.

Biochemical assays at baseline

In all the patients, blood glucose, HbA_{1c} (A1C), serum total cholesterol, triglycerides, and HDL cholesterol were measured at fasting. LDL cholesterol was calculated according to the Friedwald formula.

Follow-up

A follow-up procedure was decided on by the investigators and included at least one cardiovascular examination once a year. Most of the patients were followed up by our hospital departments. For those who were followed by a general practitioner or a cardiologist, information was obtained from their physicians. The case report files of the patients who were hospitalized in other departments were obtained. The patients who had not been recently examined in our departments were contacted by letter and phone to obtain an assessment of cardiovascular signs and symptoms and a 12-lead ECG. For the patients who died, the cause of death was documented with the help of the patient's family and general practitioner.

The following were considered to be major cardiac events: death of cardiac origin (sudden death or death caused by myocardial infarction or congestive heart failure) and nonfatal myocardial infarction. We considered unstable angina, congestive heart failure, resuscitation from ventricular tachycardia/fibrillation

of ischemic origin, and a secondary need for coronary revascularization as other (soft) cardiac events. Myocardial infarction was considered to be a major event if it was documented by ECG and/or enzyme criteria, whether the patient was hospitalized or not. Silent myocardial infarction was defined by the appearance of new Q waves (duration \geq 0.04 s, depth \geq 0.5 mV) on at least two contiguous leads on the ECG performed during the follow-up. Unstable angina was defined as reversible ischemic ST changes, i.e., ST segment depression or elevation \geq 1 mm, with clinical symptoms and a normal serum creatinine kinase level. Congestive heart failure was defined by the occurrence of an acute pulmonary edema requiring an hospitalization and with supportive documentation such as chest radiograph.

Sample size

In this population of diabetic patients with other cardiovascular risk factors, we hypothesized that the total rate of cardiac events over a 4-year follow-up would be 8% in the group without SMI and 20% in the group with SMI. Therefore, to reach a statistically significant difference between the two groups with a power of 80%, 200 patients without SMI and 100 patients with SMI had to be included.

Statistical analyses

Data are shown as means \pm SD values and percentages. Continuous variables were compared with the Student's *t* test or Mann-Whitney and Kruskal-Wallis non-parametric tests (according to the gaussian or nongaussian distribution) and categorical data with the Pearson χ^2 test.

We used a χ^2 automatic interaction detection algorithm to determine the cut-off point for age providing two independent samples having the optimum difference with regard to percentages of events.

The associations between SMI or cardiac events and binary clinical factors were tested with the Fisher's exact test into 2 \times 2 cross tabulations, and the strength of associations measured by odds ratios (ORs) and their 95% CI. The ORs were computed in various clinical categories. Survival rates were compared with Kaplan-Meier curves and the log-rank test. We performed Cox regressions analyses and computed hazard ratios (HRs) with their 95% CI to identify the significant and independent risk factors of cardiac events.

Table 1—Clinical and biological parameters in the whole series of 370 patients and in the patients with or without SMI or cardiac events

	All patients	Patients with SMI	Patients without SMI	Patients with cardiac events	Patients without cardiac events
n	370	131	239	53	317
Age (years)	57.3 ± 10.6	58.6 ± 10.1*	54.9 ± 10.1	59.8 ± 10.1§	55.6 ± 10.2
Men (%)	233 (63.0)	101 (77.1)†	132 (55.2)	35 (66.0)	201 (63.4)
Duration of diabetes (years)	16.0 ± 9.9	14.9 ± 9.0	16.5 ± 10.3	16.1 ± 11.8	16.0 ± 9.5
Type of diabetes (type 1/type 2)	45/325	14/117	31/208	4/49	41/276
Smoking (%)	41.4	44.3	39.7	43.4	41.0
Hypertension (%)	63.2	66.4	61.5	62.3	63.4
BMI (kg/m ²)	27.8 ± 5.6	27.8 ± 5.0	27.7 ± 5.8	27.9 ± 5.4	27.7 ± 5.5
Fasting glycemia (mmol/l)	9.80 ± 4.06	9.54 ± 3.70	9.82 ± 4.11	9.39 ± 3.30	9.76 ± 4.04
A1C (%)	8.07 ± 1.94	7.88 ± 2.13	8.10 ± 1.86	8.11 ± 1.67	8.01 ± 2.01
Cholesterol (mmol/l)	5.65 ± 1.25	5.60 ± 1.42	5.67 ± 1.15	5.73 ± 1.45	5.63 ± 1.22
Triglycerides (mmol/l)	2.07 ± 1.50	2.29 ± 1.81†	1.90 ± 1.27	2.58 ± 1.87§	1.95 ± 1.40
HDL cholesterol (mmol/l)	1.19 ± 0.43	1.11 ± 0.39‡	1.22 ± 0.44	1.15 ± 0.38	1.19 ± 0.44
LDL cholesterol (mmol/l)	4.05 ± 1.15	4.00 ± 1.19	4.06 ± 1.17	4.02 ± 1.23	4.05 ± 1.15
Nephropathy (%)	43.9	48.5	51.5	54.1	42.5

Data are means ± SD, unless otherwise indicated. * $P < 0.001$; † $P < 0.02$; ‡ $P < 0.05$ vs. patients without SMI. § $P < 0.005$ vs. patients without cardiac events. ||Urinary albumin excretion rate was measured in 312 of the 370 patients.

All probabilities were two sided, with a P value < 0.05 considered as statistically significant. Statistical analyses were performed by using SPSS 10.05 (SPSS, Chicago, IL) and STATXACT 3 (CYTEL Software, Cambridge, MA).

RESULTS

Initial assessment

A total of 370 diabetic patients were recruited (Table 1). None of the patients was taking statins, angiotensin receptor blockers, or aspirin, and 20% of them were taking ACE inhibitors.

SMI was identified in 131 of the patients (35.4%), from either an abnormal ECG stress test with ST segment depression (27 patients), abnormal myocardial perfusion imaging (95 patients), or both (9 patients). Seventy percent of the patients achieved $\geq 85\%$ of the maximum age-predicted heart rate during the ECG stress test.

The comparison of the patients with or without SMI showed that those with SMI were older, had higher triglycerides and lower HDL cholesterol levels, and the percentage of men was higher (Table 1).

According to the automatic interaction detection algorithm, 62 years was the cutoff for age which separated two samples with regard to both prevalence of SMI ($P = 0.0004$) and percentages of cardiac events (major + other cardiac events) for the patients with SMI at baseline ($P = 0.019$). Therefore, we decided to consider the more simple cutoff point of 60 years.

The prevalence of SMI was 30.2% in patients < 60 and 43.4% in patients > 60 years of age (Table 2). Considering SMI as a dependent variable and age, sex, and HDL cholesterol as independent variables, SMI and age were found to be associated with an HR of 1.037 (95% CI 1.004–1.070) ($P = 0.026$).

Follow-up

Follow-up was obtained in 100% of the patients. Follow-up duration was defined as the period of time up to the occurrence of the first cardiac event or up to the last information obtained for each patient. It was 3–89 months (mean: 38 ± 23 months). Cardiac events occurred in 53 patients (14.3%), including 38 (10.3%) major cardiac events (12 deaths of cardiac origin and 26 myocardial infarctions). Other cardiac events occurred in 15 patients (9 unstable angina, 2 congestive heart failure, and 4 coronary revascularizations).

Comparison of the patients who had a cardiac event with those who remained free of cardiac events shows that at the initial assessment, the patients with cardiac events were older and had higher triglyceride levels, and there was a trend (NS) toward a higher proportion of patients with nephropathy (Table 1). The rate of cardiac events did not differ significantly between type 1 and type 2 diabetic patients.

Of the 131 patients with SMI, 30 (22.9%) had cardiac events (22 major and 8 other events), whereas of the 239 pa-

tients without SMI, 23 (9.6%) had cardiac events (16 major and 7 other events) (Table 2). Significantly more major events occurred in patients with SMI (HR 3.00 [95% CI 1.53–5.87]; $P = 0.001$), whereas there was no difference for other events in patients with and without SMI. The Kaplan-Meier method confirmed that SMI was associated with a higher rate of major cardiac events (log rank 11.44; $P = 0.007$) (Fig. 1). Most of the cardiac events (24 of 30) occurred within the first 36 months of follow-up in the patients with SMI, whereas 11 of the 23 cardiac events occurred after 36 months in the patients without SMI. The Kaplan-Meier method confirmed that SMI was associated with a higher rate of cardiac events (log rank 13.07) ($P = 0.0003$) (Fig. 1). The HR was 2.79 (95% CI 1.54–5.04) with the Cox regression model. When age, triglycerides, and nephropathy were included as additional independent variables, the association between SMI and cardiac events remained significant, with an adjusted HR of 2.22 (95% CI 1.09–4.49) ($P = 0.027$).

Most cardiac events ($n = 32$, 64%) occurred in patients who were > 60 years of age at baseline. SMI was associated with a significant risk of cardiac events (HR 2.89 [95% CI 1.31–6.39]; $P = 0.009$) for the patients > 60 years but not for patients < 60 years (HR 1.93 [0.81–4.59] (Table 2). Of the 63 patients > 60 years of age with SMI, 15 patients (23.8%) had major cardiac events, whereas only 7 of 82 patients (8.5%) without SMI had major events. Again, significantly more ma-

major events occurred in patients with SMI (HR 3.66 [1.36–9.87]; $P = 0.010$), whereas there was no difference for other events in patients with and without SMI (Table 2).

CONCLUSIONS — The present study found a high prevalence of SMI (around 35%) in strictly asymptomatic diabetic patients with no cardiac history and with a normal 12-lead ECG at rest (type 1 SMI) but with two or more additional cardiovascular risk factors. The rate of SMI in such patients has been previously found to be up to 35% (7–14,17,18), and significant coronary stenoses on angiography have been reported in 35–73% of the diabetic patients with SMI (7,9–12,19). Regarding the discrepancy between the presence of SMI and the lack of significant coronary stenoses on angiography, some of us have provided evidence for a coronary endothelial dysfunction and a decrease in coronary reserve in the diabetic population (20,21).

The main finding of the current study is that SMI has a strong predictive value for all cardiac events with a relative risk of 2.79 and for major cardiac events (deaths of cardiac origin and nonfatal myocardial infarctions). In the literature, data are scarce on the prognostic value range of SMI in diabetic patients (11,13–16), and most of the studies include rather small numbers of patients (13–15) or also symptomatic patients (13). The substudy from the Coronary Artery Surgery Study registry showed that in patients with coronary stenoses, SMI was associated with a significantly lower 6-year survival rate in the diabetic patients than in the nondiabetic patients (59 vs. 82%) (22). The present study definitely establishes the prognostic value of SMI in diabetic patients for cardiac events. We have also recently shown that cardiac autonomic neuropathy (CAN) might be a better predictor of cardiac events than SMI and that the risk linked to CAN appears to be independent of SMI and to be higher when CAN is associated with SMI (14). This data needs to be confirmed in a large prospective follow-up study, such as the ongoing DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (17).

The clinical relevance of the adverse outcomes related to SMI is supported by the suggestion that the rate of coronary deaths in diabetic patients without previous myocardial infarction is as high as in nondiabetic patients with previous myocardial infarction (23). This is consistent

Table 2—Influence of SMI on the occurrence of all cardiac events and major and other cardiac events according to age at baseline

Patients (n)	Age (years)	Age <60 years				Age >60 years			
		Cardiac events, n (%)	OR	HR	Patients (n)	Age (years)	Cardiac events, n (%)	OR	HR
SMI–	49.5 ± 7.9	Total: 12 (7.6)	1	1	82	65.2 ± 3.8	Total: 11 (13.4)	1	1
		Major: 9 (5.7)	1	1			Major: 7 (8.5)	1	1
		Other: 3 (1.9)	1	1			Other: 4 (4.9)	1	1
SMI+	50.7 ± 7.0	Total: 9 (13.2)	1.84 (0.74–4.61)	1.93 (0.81–4.59)	63	67.1 ± 4.6	Total: 21 (33.3)	3.23 (1.42–7.35)	2.89 (1.31–6.39)
		Major: 7 (10.3)	1.91 (0.68–5.37)*	2.04 (0.76–5.47)*			Major: 15 (23.8)	3.62 (1.37–9.60)*	3.66 (1.36–9.87)*
		Other: 2 (2.9)	1.64 (0.27–10.06)†	1.60 (0.27–9.64)†			Other: 6 (9.5)	2.54 (0.68–9.51)†	2.09 (0.54–8.07)†
			NS				NS		NS

Data are means ± SD or OR or HR (95% CI). HR has been adjusted on age. P values are in Italics. *Calculated on the patients who remained free of other cardiac events. †Calculated on the patients who remained free of major cardiac events.

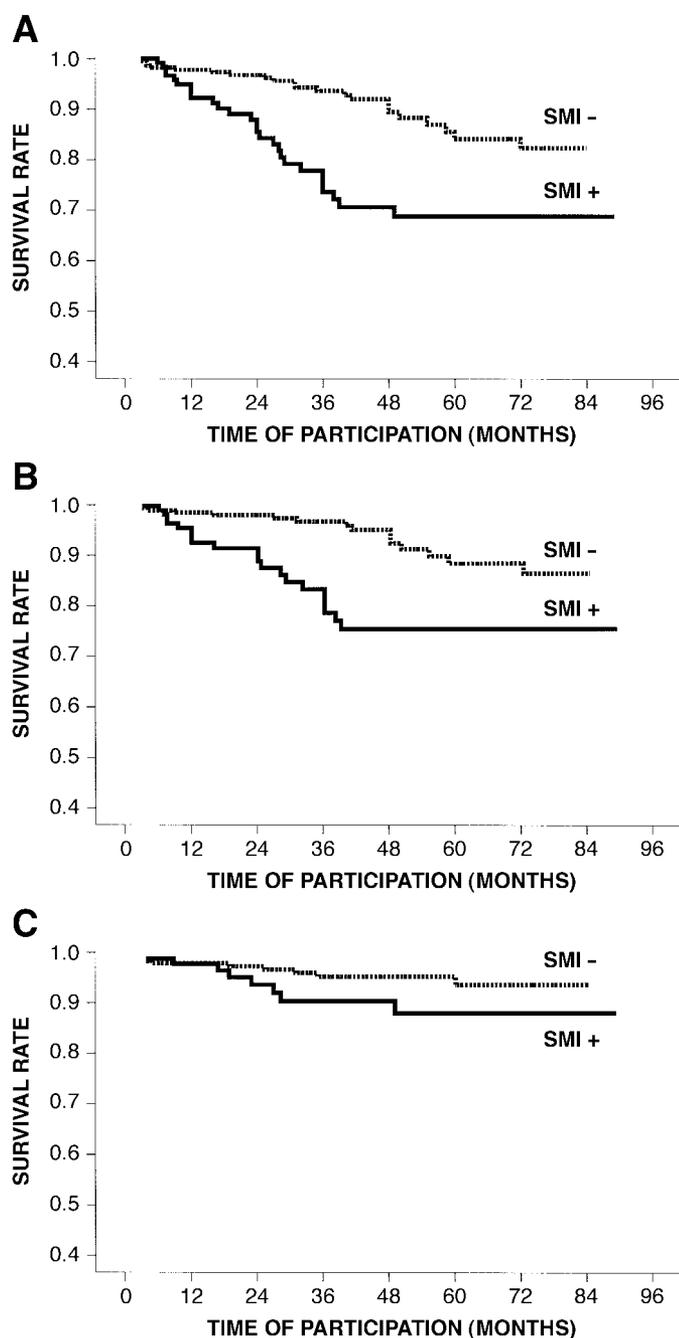


Figure 1—Kaplan-Meier analyses of the survival rates without any cardiac event (A), without major cardiac event (B), or other (C) cardiac event in the patients with (SMI+) or without (SMI-) SMI.

with a high prevalence of silent coronary heart disease in diabetic patients. However, even in our diabetic patients without SMI, the rate of cardiac events was rather high (9.6%) but consistent with their diabetes duration (mean 16.5 years) since the cardiovascular risk increases with diabetes duration (24), and possibly related to the lack of intensive preventive treatment. However, nearly half of the events occurred 36 months after the initial car-

diac assessment in these patients, which should therefore lead to a reassessment of SMI 3 years later, as recently suggested by the French guidelines (25).

Another major finding of the present study is related to the influence of age on the presence of SMI and on cardiac events in diabetic patients. The highest risk of cardiac events related to SMI (OR 3.23) was found in those >60 years of age at baseline, and a cardiac event occurred in

one-third of the patients with SMI who were >60 years of age whereas the other classical cardiovascular risk factors had no significant predictive value for cardiac events. Age has been reported in several studies to be an univariate predictor of SMI (8,15). Our present data suggest that SMI should be looked for preferably in the patients >60 years of age.

Detection of SMI is also important as its prognosis can then be improved. Indeed, medical treatments have been shown to be effective in reducing SMI episodes and adverse outcomes, including β -blocker (26) or statin treatments (27). The Steno 2 has recently shown that a multifactorial approach in high-risk type 2 diabetic patients reduced the rate of cardiovascular events by one-half (28). The application of these results to our patients >60 years of age who had SMI might have reduced theoretically the rate of cardiac events 3 years later from 33 to around 16%, which still remains very high. In addition, the results of the ACIP (Asymptomatic Cardiac Ischemia Pilot) trial suggest that revascularization, compared with medical treatment, reduced adverse outcomes at one year in patients with SMI (29). Similarly, the substudy from the Coronary Artery Surgery Study registry has shown that the 6-year survival rate of the diabetic patients with SMI is higher after coronary bypass grafting than after medical treatment in those with three coronary artery lesions or left ventricle dysfunction (22). Altogether, these data strongly suggest that in addition to optimized multifactorial medical treatment, SMI should lead to performance of a coronary angiography to undertake a revascularization procedure when possible.

In conclusion, this multicenter follow-up study clearly shows that SMI had a high predictive value for cardiac events and in particular for major cardiac events in diabetic patients. In the patients >60 years of age and with other cardiovascular risk factors, the prevalence of SMI is particularly high (43.4%), and the predictive value of SMI for cardiac events very high (OR 3.23). These two findings strongly suggest that SMI screening should be done preferably in diabetic patients >60 years old with additional cardiovascular risk factors as recently recommended by the French guidelines (25). In the future, identification of other markers of coronary artery disease may reduce the number of patients requiring SMI detection. Finally, new trials are required to evaluate to what extent the adverse outcomes may

be reduced by medical treatment and/or coronary revascularization procedures specifically in diabetic patients with type 1 SMI.

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