CLINICAL RESEARCH

Intensive cardiovascular risk factors therapy and prevalence of silent myocardial ischaemia in patients with type 2 diabetes

Traitement intensif des facteurs de risque cardiovasculaire et prévalence de l’ischémie myocardique silencieuse chez le diabétique de type 2

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KEYWORDS
Cardiovascular risk factors;
Coronary artery disease;
Diabetes mellitus;
Prevention;
Silent myocardial ischaemia

Summary
Background. — Screening for silent myocardial ischaemia (SMI) is a controversial strategy undergoing intensive risk factor therapy.
Aims. — To assess the prevalence of SMI and coronary artery disease (CAD) in asymptomatic type 2 diabetic patients at high cardiovascular risk (two additional risk factors or more) and undergoing long-term intensive risk factor therapy and tight glycaemic control.
Methods. — SMI screening, using isotopic or echographic stress tests, was carried out in 122 asymptomatic type 2 diabetic patients at high cardiovascular risk and undergoing long-term

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intensive risk factor therapy. Coronary angiography was proposed if SMI was detected. Long-term follow-up data on death, myocardial infarction and revascularization were obtained by telephone call or clinical review.

Results. — The mean age was $65 \pm 6$ years and 74% of patients were men. The mean duration of diabetes was $15 \pm 9$ years. The mean number of additional risk factors was 2.9, 32% of patients had microalbuminuria and 12% had peripheral arterial disease. SMI was detected in 20 (16%) patients. Seven (6%) patients had significant CAD treated successfully by angioplasty ($n=6$) or bypass surgery ($n=1$). The positive predictive value of the non-invasive screening test for the diagnosis of significant CAD (stenosis > 50%) was 39%. The event rate was very low (1.6%) at 2-year follow-up.

Conclusion. — Long-term intensive risk factor therapy in high-risk patients with type 2 diabetes is associated with low prevalence of SMI and detected CAD. Optimal medical therapy and revascularization of significant CAD are associated with a low cardiovascular event rate at two years.

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Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>SMI</td>
<td>Silent myocardial ischaemia</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>99mTc-sestamibi</td>
<td>Technetium-99m-methoxyisobutyl isonitrile</td>
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Introduction

The prevalence of type 2 diabetes mellitus is increasing worldwide [1]. Cardiovascular events, often atypical in feature, are the main cause of death in this population. The prevalence of SMI is higher in these patients than in non-diabetic patients and has a poorer prognosis [2].

To prevent adverse cardiovascular events, the SFC/ALFEDIAM and the American College of Cardiology/American Diabetes Association (ACC/ADA) have provided guidelines for the detection of asymptomatic CAD in patients with type 2 diabetes [3,4].
Despite a number of trials involving patients with type 2 diabetes, the usefulness of SMI screening remains controversial, especially in the context of intensive risk factor therapy [5]. The need for systematic preoperative coronary angiography and revascularization in high-risk patients is also inconclusive [6,7]. Moreover, several studies have failed to show any prognostic benefit of systematic revascularization for stable CAD [8,9]. Whether these results can be extrapolated to patients with type 2 diabetes is unknown, although the ongoing Bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial may bring some answers [10].

The aim of our study was to assess the prevalence of SMI and CAD in patients with type 2 diabetes selected according to SFC/ALFEDIAM guidelines in the setting of intensive risk factor therapy and tight glycaemic control.

Patients and methods

Patients

One hundred and forty-six patients with type 2 diabetes mellitus were included prospectively between November 2003 and October 2006. The screening was performed in consultation in the Department of Diabetology. The population comprised consecutive patients selected for their high-risk profile according to specific inclusion and exclusion criteria (Table 1). All patients had been receiving long-term intensive treatment of atherosclerotic risk factors since 2001, with stepwise implementation of behaviour modification and pharmacological therapy targeting hyperglycaemia, hypertension and dyslipidaemia [11]. The treatment objectives were glycosylated haemoglobin (HbA1c) less than 6.5%, blood pressure less than 130/80 mmHg, and LDL cholesterol plasma concentration less than 1 g/L. Daily life activity and smoking cessation were encouraged strongly.

Diabetes was diagnosed according to WHO criteria [12]. Latent autoimmune diabetes and secondary diabetes were ruled out for all patients. Associated cardiovascular risk factors were defined as follows: age over 55 years for men and over 60 years for women, obesity (body mass index > 30 kg/m²), high blood pressure (systolic > 140 mmHg and/or diastolic > 80 mmHg), dyslipidaemia (LDL cholesterol > 1.3 g/L, HDL cholesterol < 0.35 g/L or triglycerides > 1.5 g/L), active smoker, and family history of premature CAD (< 55 years for men, < 60 years for women). All patients underwent evaluation of diabetes complications, including fundoscopy, measurement of microalbuminuria and proteinuria during a 24-hour urine collection and ultrasound visualization/examination of peripheral arteries. Microangiopathy was defined as the presence of panphotocoagulated retinopathy and/or microalbuminuria (> 300 mg/day). All patients gave informed consent and the study was approved by the local institutional ethics committee.

Study design

Patients underwent stress thallium-201 SPECT or DE. Treatment with nitrates, betablockers and calcium channel blockers was stopped more than or equal to 48 h before the tests. Coronary angiography was offered to all patients if myocardial ischaemia was detected by a non-invasive test. All patients with significant CAD (greater or equal to 50% stenosis in greater or equal to one major vessel or branch) suitable for revascularization were treated systematically with angioplasty or surgery as appropriate. Aspirin

<table>
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<tr>
<th>Table 1</th>
<th>Inclusion and exclusion criteria.</th>
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<td>Inclusion criteria</td>
<td>Type 2 diabetes</td>
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<tr>
<td></td>
<td>&gt; 60 years (men), &gt; 55 years (women)</td>
</tr>
<tr>
<td></td>
<td>No clinical symptoms of CAD</td>
</tr>
<tr>
<td></td>
<td>AND peripheral or carotid occlusive arterial disease</td>
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<tr>
<td></td>
<td>OR microalbuminuria (&gt; 300 mg/day)</td>
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<tr>
<td></td>
<td>OR abnormal ECG (repolarization change, bundle branch block)</td>
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<td></td>
<td>OR heart failure (LVEF &lt;40%)</td>
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<td></td>
<td>OR ≥2 of the following risk factors:</td>
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<tr>
<td></td>
<td>High blood pressure, defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 80 mmHg on ≥ 2 occasions, or antihypertensive therapy</td>
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<td>Dyslipidaemia, defined as plasma concentration of LDL cholesterol &gt; 1.3 g/L, HDL cholesterol &lt; 0.35 g/L, triglycerides &gt; 1.5 g/L, or lipid-lowering therapy</td>
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<td>Obesity (body mass index &gt; 30 kg/m²)</td>
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<td></td>
<td>Family history of premature CAD</td>
</tr>
<tr>
<td></td>
<td>Active smoker (&gt; 10 cigarettes per day)</td>
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<td>Retinopathy (panphotocoagulated)</td>
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<table>
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<tr>
<th>Exclusion criteria</th>
<th>Symptoms of CAD</th>
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<tr>
<td>History of CAD (previous myocardial revascularization, coronary angioplasty or surgery)</td>
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<tr>
<td>Acute coronary syndrome</td>
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CAD: coronary artery disease; ECG: electrocardiogram; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LVEF: Left ventricular ejection fraction
greater than 3 [13,14]. considered to be abnormal if the summed stress score was scale ranging from 0 (normal) to 4 (no uptake). A test was segment model and their severity was graded on a 5-point nuclear cardiologists for assessment of myocardial perfusion (50 s/projection), with 16 frames/cycle.

All acquisitions were reviewed by two experienced nuclear cardiologists for assessment of myocardial perfusion defects. The extent of the defects was quantified on a 17-segment model and their severity was graded on a 5-point scale ranging from 0 (normal) to 4 (no uptake). A test was considered to be abnormal if the summed stress score was greater than 3 [13,14].

DE
A standard echocardiographic evaluation with tissue harmonic imaging (ACUSON Sequoia C256, Siemens Medical Solutions USA, Inc., Malvern, PA, USA) was carried out for all patients. A stress DE test was performed using a standard incremental dosing protocol from 5—40 μg/kg per minute intravenously [15]. As the last dose was given, an intravenous bolus of atropine 0.25 mg (up to 1 mg) was added to achieve maximum heart rate. Heart rate and rhythm were monitored continuously and blood pressure and a 12-lead ECG were recorded every 3 min. Symptoms were documented.

Images were digitized online into a quad-screen display, and were interpreted by an experienced observer trained in the technique. Analyses were performed in the four standard imaging planes: parasternal long-axis, parasternal short-axis, apical four-chamber and apical two-chamber views [16]. Segmental wall motion was assessed with a 16-segment model and graded visually as normal, hypokinetic, akinetic, or dyskinetic. Myocardial ischaemia was identified in the presence of a new or worsening wall motion abnormality in two or more contiguous segments.

Coronary angiogram
Patients with SMI underwent coronary angiography within one week of isotopic or echocardiographic testing. After intracoronary injection of linsidomine 1 mg, digital computer-assisted calipers (DCI, Philips Healthcare, Andover, MA, USA) were used to measure stenotic seg-
ments of the arteries in the view showing the most severe cross-sectional narrowing. Coronary arteries were considered to be angiographically normal (without irregularities), unobstructed (< 25% diameter stenosis) or obstructed (> 50% diameter stenosis in a segment with a normal diameter ≥ 1.5 mm) [17].

Follow-up
Follow-up focused on the incidence of death, myocardial infarction and revascularization. In patients who had undergone coronary angioplasty, stress SPECT was performed systematically six months after the procedure. A new coronary angiogram was performed in patients who experienced occurrence of clinical symptoms during follow-up or in whom stress SPECT demonstrated ischaemia that was either severe or involved new segments. Restenosis was diagnosed when a narrowing of more than 50% of vessel diameter was found at the site of the previous dilatation. Clinical restenosis was defined as recurrent myocardial ischaemia related to angiographic restenosis. Indications for a new revascularization procedure were either the appearance of a new significant coronary artery stenosis not present on the initial angiogram or restenosis at a site of the previous dilatation.

Statistical analysis
Continuous variables are presented as mean and standard deviation (S.D.). Categorical data are presented as numbers and percentages. Univariate analyses were performed using the chi-square test for categorical data and analysis of variance for continuous variables. A multivariable analysis was performed using a multiple regression model including all univariate variables with a p-value < 0.1.

Results
Of the 146 patients included in the study, 122 achieved an analysable stress test. Fifty-nine patients underwent DE and 63 underwent SPECT. Eighteen patients refused to participate in a stress test. Adequate DE could not be performed in six patients: three with poor echogenicity, two with aortic stenosis and one with high pretest blood pressure.

Clinical characteristics
The mean age of the study population was 65 years and most patients (74%) were men. The mean duration of diabetes was 15 years, 40% of patients were treated with insulin and 60% received oral antidiabetic therapy alone. The study population was at high cardiovascular risk with a mean of 2.9 additional conventional risk factors: 32% had microalbuminuria and 12% had peripheral arterial disease. Only 15% of patients had an abnormal ECG.

Prevalence of SMI and detected CAD
SMI was detected by SPECT or DE in 20 (16%) patients. Of the 63 patients who underwent SPECT, 12 (19%) had SMI. The mean maximum predicted heart rate achieved was 86%. The stress test took the form of exercise in
49% of patients, intravenous infusion of dipyridamole in 10% of patients, and a combination in 41% of patients. Of the 59 patients who underwent DE, eight (14%) had SMI. Two patients had intraventricular gradient, one patient had a non-sustained ventricular tachycardia and one patient had transient atrial fibrillation during dobutamine infusion. Three patients did not reach 85% of the maximum predicted heart rate despite having received the highest doses of dobutamine and atropine. The mean maximum predicted heart rate achieved was 92%, with a mean of 24 μg/kg per minute of dobutamine plus 0.75 mg of atropine.

Table 2 shows the baseline characteristics of the patients according to the presence or absence of SMI. In the univariate analysis, only the duration of diabetes was associated significantly with SMI. The multivariable analysis, which included all variables with a p-value < 0.1 on univariate analysis, indicated that the duration of diabetes was the only independent predictor of SMI (p = 0.02).

Two of the 20 patients with SMI declined coronary angiography. In the remaining 18 patients coronary angiography revealed significant coronary stenoses in seven patients, non-significant lesions in four patients, and was normal in seven patients. Thus, the positive predictive value of the non-invasive stress test (SPECT or DE) to detect significant coronary stenosis was 39%. The seven patients with significant stenosis (three with single-vessel disease and four with multivessel disease) were compared with the patients without SMI (n = 102) or without significant coronary stenosis evident on angiogram (n = 11). No independent predictor was found on multivariable analysis.

### Follow-up

The long-term intensive treatment of modifiable atherosclerotic risk factors was continued during clinical follow-up in all patients, according to current guidelines. Six patients with significant coronary stenosis were treated by coronary angioplasty with drug-eluting stents and one patient underwent coronary artery bypass graft surgery. Long-term clinical follow-up data were available in 121 (99%) patients. Only two cardiovascular events occurred during follow-up. One patient with an initial negative stress DE test had a myocardial infarction. Another patient with an initial negative stress DE test developed angina two years after screening and benefited from percutaneous coronary intervention. One patient with a negative stress SPECT test died from cancer (non-cardiac death). Thus, the cardiovascular event rate was 1.6% at a mean follow-up duration of 24 ± 10 months.

### Discussion

Our study has shown a 16% prevalence of SMI in a population of high-risk patients with asymptomatic type 2 diabetes receiving long-term intensive treatment of cardiovascular risk factors.
risk factors. We found that SMI was associated with the duration of diabetes. Only 6% of patients with SMI had significant CAD on angiogram; percutaneous coronary intervention was the principal revascularization therapy for patients with CAD. The cardiovascular event rate was very low (1.6%) at two-year follow-up.

The prevalences of SMI and detected CAD in our study are much lower than those reported previously in patients receiving conventional care for cardiovascular risk factors. The prevalence of SMI in the asymptomatic type-2 diabetic population has been investigated in a number of studies, and has been shown to be three to six times higher in this setting than in non-diabetic patients [18]. The presence of SMI is strongly indicative of a poor prognosis [2,19]. The SFC/ALFEDIAM and the ADA/ACC have therefore produced strict guidelines that recommend SMI screening for diabetic patients with peripheral or carotid disease or two or more additional risk factors [3,4].

In diabetic patients, the reported prevalence of SMI varies from 12 to 62%; this discrepancy can be explained in part by differences in patient selection and choice of stress test [20]. In the large Milan Study on Atherosclerosis and Diabetes (MiSAD), in which 925 asymptomatic type 2 diabetic patients were enrolled, the prevalence of SMI assessed by stress ECG treadmill test was a low 12%, but the screened population was at very low risk (there was no requirement for additional risk factors for enrolment) [21]. Likewise, Janand-Delenne et al. reported an 18% prevalence of SMI in patients with type 2 diabetes who had only one or more additional risk factors [22]. In a similar population, Cosson et al. reported a 33% prevalence of SMI using SPECT [23]. When the current recommended inclusion criteria are adhered to — as in our study — the prevalence of SMI is found to be much higher. Thus, Valensi et al. found a 30% prevalence of SMI using a triple modality screening in 132 patients with asymptomatic type 2 diabetes, and Vanzetto et al. found a 37% prevalence of reversible SPECT defects among 158 patients [2,24]. Among diabetic patients with peripheral vascular disease, the prevalence of SMI has been found to be as high as 57% [25]. More recently, the ongoing DIAD study showed a high 22% prevalence of SMI assessed by SPECT in 522 asymptomatic diabetic patients, despite a low-risk profile (only 60% of patients fulfilled the ADA/ACC criteria) [26]. In our study, the 16% prevalence of SMI in intensively treated high-risk patients with asymptomatic type 2 diabetes is lower than that reported in previous studies of patients receiving conventional risk factor care. These results emphasize the benefit of intensive therapy in type 2 diabetes.

We have reported previously our first experience of systematic SMI screening (SPECT ± DE) of high-risk patients with asymptomatic type 2 diabetes [17]. At that time, cardiovascular risk factors were treated less intensively. Compared with the 100 patients in our previous study, the 122 patients in this study have benefited from long-term intensive therapy with better control of cardiovascular risk factors (blood pressure 133/73 vs 139/76 mmHg, LDL cholesterol 1.0 vs 1.2 g/L) and glycaemia (HbA1c 7.7% vs 9.4%). Despite the higher cardiovascular risk profile of patients in this study (older, 65 vs 61 years; a higher proportion of men, 74% vs 53%; a trend for a higher mean number of risk factors, 2.9 vs 2.6), we found a lower frequency of SMI (16% vs 62%) and detected CAD (6% vs 25%) than in our earlier study. These findings suggest that strict glycaemic control and intensive treatment of cardiovascular risk factors are associated with lower prevalences of SMI and CAD in patients with asymptomatic type 2 diabetes at high risk of coronary disease. However, this is an observational comparison that was not prespecified.

We have reported a surprisingly low cardiovascular event rate (0.8%/year) in this high-risk population, with no cardiovascular death; this is well below the almost 3% per year rate observed in the overall diabetic population [27], and the greater than 40% incidence of coronary heart disease at 10 years reported in diabetic patients with multiple risk factors [28]. The mortality rate is also lower than the reported 1.2% annual cardiovascular death rate in diabetic patients with three associated risk factors [29]. These observations probably reflect the global improvement in care of diabetes as emphasized in the European action on secondary prevention through intervention to reduce events (EUROASPIRE) surveys [30]. It is now well established that patients with diabetes benefit from intensive cardiovascular risk factor prevention, i.e. statins for LDL cholesterol less than 1 g/L, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists for blood pressure < 130/80 mmHg, and tight glucose control (HbA1C < 6.5%) [11]. In our study, no event occurred in the group with SMI in which, the seven patients (6%) with detected significant CAD underwent myocardial revascularization.

Systematic screening for SMI among high-risk patients with asymptomatic type 2 diabetes is a controversial strategy. The higher prevalence of SMI in this group than in the general population, and the poorer prognosis with which SMI is associated, provide a strong case in favour of systematic screening. Betablockers are effective in reducing ischaemia during daily life and cardiovascular adverse events [31]. In the Asymptomatic cardiac ischemia pilot (ACIP) study, revascularization led to an improvement in the event-free survival rate in patients with asymptomatic diabetes [32]. Revascularization before renal transplantation has also been shown to reduce the occurrence of adverse cardiovascular events in asymptomatic diabetic patients with end-stage renal failure [33]. However, these trials involved small sample sizes, and were conducted several years ago, before the widespread use of intensive risk factor therapy and tight glycaemic control according to recent guidelines. More recently, Faglia et al. reported a significant 26% risk reduction in adverse cardiovascular events at 54 months in a screened group compared with a non-screened group [34]. This study is the first — albeit with a small sample size — to show a prognostic benefit of systematic screening, but the results need to be confirmed in a large study.

Some concerns have arisen about the usefulness of revascularization for stable CAD [8,9]. The recent Clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) study showed that interventional therapy with angioplasty was no more beneficial than ischaemia — or symptom-driven therapy in stable CAD patients [35]. However, it must be emphasized that the population was highly selected (only 7% of the initial population were randomized) and that one-third of the patients in the group who received optimal medical therapy alone underwent percutaneous revascularization during follow-up.
Before vascular surgery, no reduction in cardiovascular adverse event rate was observed after preoperative myocardial revascularization in high-risk asymptomatic patients (> 30% of whom had type 2 diabetes) [6,7]. Furthermore, a cost analysis has reported a higher cost and a higher cardiovascular event rate for the screening strategy compared with an unconditional treatment strategy [5]. But it must be stressed that statin allocation (statin therapy only when SMI detected) was not integrated into standard prevention care in type 2 diabetes in that analysis.

Our results are consistent with those of the Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes (STENO-2) study, in which 160 patients with type 2 diabetes and microalbuminuria were randomized to receive conventional or intensive treatment of cardiovascular risk factors. The mean duration of follow-up was 7.8 years [36]. The authors reported a 50% reduction in the cardiovascular event rate (cardiovascular death, non-fatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, non-fatal stroke, amputation as a result of ischaemia, or vascular surgery for peripheral atherosclerotic artery disease) in the intensive risk-factor treatment group compared with the conventional care group. Thus, only five patients need to be treated intensively during this period to prevent one major adverse cardiovascular event.

In summary, among intensively treated patients with type 2 diabetes, we found that the prevalence of SMI was low (16%), that 94% of patients had no detected CAD, and that the cardiovascular event rate was less than 2% at a 2-year follow-up. Long-term intensive cardiovascular risk factor therapy and tight glycaemic control are associated with low prevalences of SMI and detected CAD, and a very low cardiovascular event rate when revascularization of significant CAD is added to optimal medical therapy. The low rate of revascularization (6%) in this study underlines the importance of the contribution that intensive risk-factor treatment can make in the achievement of a good prognosis for these patients.

The benefit of detection and treatment of SMI in high-risk diabetic patients will be confirmed by randomized studies that are currently ongoing, and which should bring some clarification to the issue of SMI screening (the DIAD study) and to the issue of revascularization (the BARI-2 study).

References