A randomized study comparing isotope and echocardiography stress testing in the screening of silent myocardial ischaemia in type 2 diabetic patients

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Abstract

Aims. – This study aimed to compare the positive predictive value (PPV) of stress myocardial scintigraphy (SPECT) and of dobutamine echocardiography (DE) in the diagnosis of significant coronary artery stenosis (CAD) in asymptomatic type 2 diabetic patients, and to assess long-term clinical outcomes according to silent myocardial ischaemia (SMI) screening.

Methods. – A total of 204 asymptomatic type 2 diabetic patients at high cardiovascular (CV) risk were prospectively randomized to undergo either SPECT (n = 104) or DE (n = 100). Coronary angiography was proposed in cases of SMI, with revascularization of suitable lesions. Intensive treatment of CV risk factors was prescribed for all patients. Death and myocardial infarction (MI) were recorded during the 3-year follow-up.

Results. – Clinical characteristics were similar in the two testing groups. The prevalence of SMI and significant CAD were 13% and 4%, respectively, in the SPECT group vs 11% and 5%, respectively, in the DE group (not significant [NS]). The PPV for the detection of significant CAD was 29% for SPECT and 45% for DE (NS). Seven patients (3%) underwent initial revascularization. The 3-year rate of CV death and MI was 2.5%, and similar in both groups.

Conclusion. – Rates of SMI and significant CAD in asymptomatic high-risk type 2 diabetic patients receiving intensive care of risk factors are low, and SPECT and DE are similar in the detection of SMI and CAD. Coronary revascularization and intensive CV risk-factor therapy are associated with a low rate of adverse CV events at 3 years, whichever stress test was used.

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Keywords: Type 2 diabetes; Silent myocardial ischaemia; Screening; Stress myocardial scintigraphy; Dobutamine echocardiography; Cardiovascular death; Prospective study; Positive predictive value

Résumé

Étude randomisée comparant échocardiographie et scintigraphie de stress dans le dépistage de l’ischémie myocardique silencieuse chez les diabétiques de type 2.

Objectif. – Comparer la valeur prédictive positive de la scintigraphie myocardique de stress (SPECT) et l’échocardiographie sous dobutamine (ED) dans le diagnostic de sténoses coronaires significatives (CAD) chez les diabétiques de type 2 (DT2) asymptomatiques ; comparer le pronostic clinique à long terme selon la méthode de dépistage.

Méthodes. – Deux cent quatre patients asymptomatiques, DT2 à haut risque cardiovasculaire, ont été randomisés entre SPECT (n = 104) et ED (n = 100). Une coronarographie a été réalisée en cas d’ischémie myocardique silencieuse (IMS), avec revascularisation si les lésions étaient accessibles. Les facteurs de risque étaient traités de manière intensive. Le suivi clinique a porté sur le taux de décès de cause cardioïque et d’infarctus à trois ans.

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**Résultats.** – Les caractéristiques cliniques étaient comparables dans les deux groupes. La prévalence de l’IMS et de la CAD était respectivement de 13 et 4 % dans le groupe SPECT, et de 11 et 5 % dans le groupe ED (NS). Les valeurs prédictives positives pour la détection de CAD significative étaient de 29 % pour la SPECT et 45 % pour l’ED (NS). Une revascularisation initiale a été réalisée chez sept patients (3 %). Le taux de décès-infarctus à trois ans était de 2,5 %, identique dans les deux groupes.

**Conclusions.** – Les fréquences d’IMS et de CAD significatives chez les DT2, asymptomatiques, avec traitement intensif des facteurs de risque sont faibles. SPECT et ED sont comparables en termes de détection d’IMS et de CAD. La revascularisation coronaire et le traitement intensif des facteurs de risque sont associés à un faible taux d’événement cardiaque à trois ans, quel que soit le test utilisé.

**Mots clés :** Diabète de type 2 ; Ischémie myocardique silencieuse ; Dépistage ; Étude prospective ; Décès cardiovasculaires ; Scintigraphie myocardique de stress ; L’échocardiographie du stress ; Valeur prédictive

### 1. Introduction

La prévalence de type 2 diabetes est dramatiquement augmentant de plus en plus de la population. Les événements cardiaques, souvent de type atypique, représentent le principal facteur de mortalité dans cette population. La prévalence de l'ischémie myocardique silencieuse (SMI) est plus élevée chez les patients diabétiques et est associée à un mauvais pronostic [2].

Pour prévenir les événements cardiaques, les directives actuelles recommandent la détection d'ischémie asymptomatique de l'artère coronaire (CAD) chez des patients diabétiques à haut risque [3,4]. L'électrocardiographie (ECG) de stress est recommandée, mais est généralement inconcluante dans les cas de patients diabétiques. Cependant, la contribution de l'échocardiographie de stress (SPECT) et de l'échocardiographie de stress (DE) est encore à l'étape de l'établissement.

Bien que les résultats de nombreuses études impliquant des patients diabétiques utilisant SMI, la pertinence de l'échocardiographie de stress dans le contexte d'un traitement des facteurs de risque [5,6]. En outre, plusieurs études ont recherché une bénéfice systématique dans le cas de l'ischémie asymptomatique de l'artère coronaire (CAD) chez des patients diabétiques à haut risque [7-9]. Cependant, la majorité de ces études excluent des patients à haut risque, comme ceux avec sténose de la valve aortique, sténose de trois vaisseaux ou ischémie ubiquitaire [6,7-9].

Les caractéristiques des patients de cette étude étaient comparables. La prévalence de l'IMS et de la CAD était respectivement de 13 et 4 % dans le groupe SPECT et de 11 et 5 % dans le groupe ED (NS). Les valeurs prédictives positives pour la détection de CAD significative étaient de 29 % pour le SPECT et 45 % pour l’ED (NS). Une revascularisation initiale a été réalisée chez sept patients (3 %). Le taux de décès-infarctus à trois ans était de 2,5 %, identique dans les deux groupes.

**2. Methods**

#### 2.1. Patients

Un total de 204 patients avec type 2 diabetes were prospectivement recruited between November 2003 and September 2008 from the diabetes department of Pitié-Salpêtrière Hospital in Paris, France. The inclusion and exclusion criteria used are listed in Table 1.

Diabetes was diagnosed according to the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [10]. Patients with latent autoimmune diabetes in adults and secondary diabetes were excluded. Associated cardiovascular risk factors were defined as: age > 55 years for men and > 60 years for women; current smoking; family history of premature CAD (< 55 years for men, < 65 years for women); obesity; high blood pressure; and dyslipidaemia (Table 1). In addition, all patients underwent evaluation for diabetes complications, including fundoscopy, microalbuminuria and proteinuria assays of 24-h urine samples, and ultrasound visualization/examination of peripheral arteries. Severe microangiopathy was defined as the presence of panphotocoagulation and/or macroproteinuria (> 300 mg/day). Peripheral (or carotid) arterial disease was defined as at least 50% stenosis in one or more vessel on Doppler imaging. All patients gave their informed consent to participate, and the study was approved by the local institutional ethics committee.

**Table 1**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with type 2 diabetes, &gt; 55 years (men) or &gt; 60 years (women) of age, with no clinical symptoms of coronary artery disease AND Heart failure (LVEF &lt; 40%) OR</td>
<td>Diabetes was diagnosed according to the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [10]. Patients with latent autoimmune diabetes in adults and secondary diabetes were excluded. Associated cardiovascular risk factors were defined as: age &gt; 55 years for men and &gt; 60 years for women; current smoking; family history of premature CAD (&lt; 55 years for men, &lt; 65 years for women); obesity; high blood pressure; and dyslipidaemia (Table 1). In addition, all patients underwent evaluation for diabetes complications, including fundoscopy, microalbuminuria and proteinuria assays of 24-h urine samples, and ultrasound visualization/examination of peripheral arteries. Severe microangiopathy was defined as the presence of panphotocoagulation and/or macroproteinuria (&gt; 300 mg/day). Peripheral (or carotid) arterial disease was defined as at least 50% stenosis in one or more vessel on Doppler imaging. All patients gave their informed consent to participate, and the study was approved by the local institutional ethics committee.</td>
</tr>
</tbody>
</table>

**Conclusions.** – Les fréquences d’IMS et de CAD significatives chez les DT2, asymptomatiques, avec traitement intensif des facteurs de risque sont faibles. SPECT et ED sont comparables en termes de détection d’IMS et de CAD. La revascularisation coronaire et le traitement intensif des facteurs de risque sont associés à un faible taux d’événement cardiaque à trois ans, quel que soit le test utilisé.

**Mots clés :** Diabète de type 2 ; Ischémie myocardique silencieuse ; Dépistage ; Étude prospective ; Décès cardiovasculaires ; Scintigraphie myocardique de stress ; L’échocardiographie du stress ; Valeur prédictive
calcium-channel inhibitors were stopped at least 48 h before the tests.

Coronary angiography was offered to all patients with myocardial ischaemia as a non-invasive test. All patients with significant coronary disease (≥ 50% stenosis in one or more major vessel or branch) suitable for revascularization were systematically treated by angioplasty or surgery as appropriate. Aspirin (100 mg/day) was given to all patients except those with a normal coronary angiography, and beta-blockers were given to all patients with myocardial ischaemia and coronary disease.

Intensive treatment of atherosclerosis risk factors had to have been prescribed for more than 3 years before inclusion in the present study, and was continued during the entire clinical follow-up period in all patients in accordance with the current guidelines, with stepwise implementation of behavioural modifications and pharmacological therapy targeting hyperglycaemia, hypertension and dyslipidaemia. Objectives were HbA1c values < 6.5%, blood pressure < 130/80 mmHg, low-density lipoprotein (LDL)-cholesterol plasma concentrations < 1.0 g/L and triglyceride plasma concentrations < 1.50 g/L.

Long-term follow-up data were obtained by clinical review or serial telephone interviews. Clinical events were corroborated by primary-source documentation. The primary endpoints were the positive predictive value (PPV) of SPECT and of DE for the detection of significant CAD. Secondary endpoints were prevalence of SMI, prevalence of CAD and the 3-year rate of cardiac death/myocardial infarction (MI), according to the stress test used.

2.3. Non-invasive stress testing

2.3.1. Myocardial perfusion imaging

Stress protocol: a symptom-limited exercise protocol was performed, using a cycloergometer, with or without dipyridamole infusion (0.7 mg/kg over 4 min), if the expected maximum heart rate achievable by the patient was < 85% of the predicted maximum heart rate. 99mTc-sestamibi was injected at the time of peak exercise.

Myocardial perfusion imaging: ECG-gated SPECT was first performed at stress. In cases of abnormality, a rest study was performed on another day. Acquisition was performed at 45 min (stress) or 60 min (rest), after infusion of 11 MBq/kg of 99mTc-sestamibi, using a DST-XLI dual-head gamma camera (GEMS, Buc, France) equipped with low-energy/high-resolution parallel collimators. Data were acquired using a 64 × 64 matrix for 32 projections (50 s/projection) at 16 frames/cycle.

Data analysis: all acquisitions were reviewed by two experienced nuclear cardiologists, who assessed any myocardial perfusion defects. Defect extent was quantified on a 17-segment model and severity on a 5-point scale, ranging from 0 (normal) to 4 (no uptake). The stress score was the sum total of the severity scores of the 17 segments. A study was considered abnormal if the total stress score was > 3 [11]. A perfusion defect at stress was considered fixed if the severity score remained unchanged at rest, or reversible if the severity score decreased at rest.

2.3.2. Dobutamine echocardiography

A standard echocardiographic evaluation with tissue harmonic imaging was carried out in all patients (Acuson Sequoia C256, Siemens Healthcare). Dobutamine stress testing used a standard incremental-dosing protocol (from 5 to 40 mcg/kg/min intravenously) [12]. The final dose was continued while a 0.25-mg intravenous bolus of atropine (up to 1 mg) was added to achieve the maximum heart rate. Heart rate and rhythm were both continuously monitored, and blood pressure and a 12-lead ECG recorded every 3 min. All symptoms were documented.

Images were digitalized online using a Quad Screen display, and interpreted by an experienced observer specifically trained in the technique. Analyses were performed in four standard imaging planes: parasternal long-axis view; parasternal short-axis view; apical four-chamber view; and apical two-chamber view [12]. Segmental wall motion was assessed by a 16-segment model and visually graded as either normal, hypokinetic, akinetic or dyskinetic. Myocardial ischaemia was identified as the presence of new or worsening wall motion abnormality in two or more contiguous segments.

2.4. Coronary angiography

Patients with SMI underwent coronary angiography within 1 week of the isotope or echocardiography testing. Digital computer-assisted calipers (DCI Philips) were used after intracoronary SIN-1 injection (linsidomine, 1 mg) to measure the stenotic segments of the arteries in the view showing the most severe cross-sectional narrowing. Coronary arteries were considered to be angiographically either normal (no irregularities), unobstructed (stenosis < 25% of vessel diameter) or obstructed (stenosis > 50% of vessel diameter) in a segment with a normal diameter ≥ 1.5 mm [13].

2.5. Follow-up

In patients who had undergone coronary revascularization, stress testing was systematically performed 6 to 12 months after the procedure. A second coronary angiography was performed in patients who experienced clinical symptoms during the follow-up or whose stress SPECT demonstrated ischaemia that was either severe or involved new segments. Restenosis was diagnosed when a narrowing of > 50% of vessel diameter was found at the site of previous dilatation. Clinical restenosis was defined as recurrent myocardial ischaemia related to angiographic restenosis. Indications for a second revascularization procedure were either the appearance of new significant coronary artery stenosis not present on the initial angiogram or restenosis at a site of previous dilatation.

Follow-up was assessed by a phone call or clinical review focusing on the primary endpoints of cardiovascular death or
MI, and on the secondary endpoints of death due to any cause or revascularization.

2.6. Statistical analysis

Continuous variables are presented as means ± standard deviation (SD). Categorical data are presented as numbers and percentage frequencies. Univariate analyses were performed using the Chi² test for categorical data, and analysis of variance for continuous variables. The analyses were based on the intention-to-treat. A multivariate analysis was performed using a multiple regression model including, among baseline characteristics, all univariate parameters with a P value < 0.10.

The study was designed with anticipated positive SPECT and DE rates of 55% and 30%, respectively, and a 23% rate of significant CAD in each group [2,5,12,13]. With this hypothesis, anticipated PPVs for the detection of significant CAD were 42% and 76% for DE and SPECT, respectively. It was also estimated that 100 patients would be required in each group to have a power of 84% to detect the difference between DE and SPECT with a two-sided alpha of 0.05.

3. Results

Of the 204 patients included in the study (104 in the SPECT group and 100 in the DE group), 182 achieved an analyzable stress test, of whom 87 (87%) had undergone DE and 95 (91%) a SPECT (not significant, NS). Sixteen patients refused to undergo a stress test. Also, an adequate DE was not possible in four patients due to poor echogenicity, in one patient because of aortic stenosis and in one patient with high blood pressure prior to testing.

3.1. Clinical characteristics

The main characteristics of the patients in each group are presented in Table 2. No significant difference was noted at baseline between the SPECT and DE groups. In general, the study population was at high cardiovascular risk, with 2.9 further risk factors in addition to age, gender and diabetes. An abnormal ECG was found in only 13% of the patients (Q waves in a specific territory [either anterior or inferior] in seven patients, negative T waves in 11 patients, a left bundle branch block [BBB] in one patient

### Table 2

Baseline characteristics of patients screened by thallium-201 single photon emission tomography (SPECT) and dobutamine echocardiography (DE).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Total (n = 204)</th>
<th>SPECT (n = 104)</th>
<th>DE (n = 100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65 ±6</td>
<td>65 ±6</td>
<td>65 ±6</td>
<td>ns</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>154 (75)</td>
<td>79 (76)</td>
<td>75 (75)</td>
<td>ns</td>
</tr>
<tr>
<td>Risk factors, n</td>
<td>2.9 ±0.9</td>
<td>2.8 ±1</td>
<td>2.9 ±0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2 ±4.98</td>
<td>29 ±5</td>
<td>29 ±5</td>
<td>ns</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>79 (39)</td>
<td>38 (37)</td>
<td>41 (41)</td>
<td>ns</td>
</tr>
<tr>
<td>High blood pressure, n (%)</td>
<td>185 (90)</td>
<td>93 (89)</td>
<td>92 (92)</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134 ±14</td>
<td>132 ±14</td>
<td>135 ±15</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72 ±9</td>
<td>73 ±9</td>
<td>73 ±11</td>
<td>ns</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>173 (85)</td>
<td>92 (88)</td>
<td>81 (79)</td>
<td>ns</td>
</tr>
<tr>
<td>Total cholesterol, g/L</td>
<td>1.8 ±0.4</td>
<td>1.8 ±0.4</td>
<td>1.8 ±0.4</td>
<td>ns</td>
</tr>
<tr>
<td>LDL cholesterol, g/L</td>
<td>1.0 ±0.4</td>
<td>1.0 ±0.4</td>
<td>1.0 ±0.3</td>
<td>ns</td>
</tr>
<tr>
<td>HDL cholesterol, g/L</td>
<td>0.5 ±0.1</td>
<td>0.5 ±0.1</td>
<td>0.5 ±0.1</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides, g/L</td>
<td>1.4 ±0.8</td>
<td>1.4 ±0.9</td>
<td>1.3 ±0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Lipid-lowering drug therapy, n (%)</td>
<td>158 (77)</td>
<td>83 (80)</td>
<td>75 (75)</td>
<td>ns</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>133 (65)</td>
<td>69 (66)</td>
<td>64 (64)</td>
<td>ns</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>36 (17.6)</td>
<td>23 (22)</td>
<td>13 (13)</td>
<td>ns</td>
</tr>
<tr>
<td>Family history of premature CAD, n (%)</td>
<td>12 (6)</td>
<td>5 (5)</td>
<td>7 (7)</td>
<td>ns</td>
</tr>
<tr>
<td>Peripheral/carotid arterial disease, n (%)</td>
<td>31 (15)</td>
<td>17 (16)</td>
<td>14 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>Severe microangiopathy, n (%)</td>
<td>38 (19)</td>
<td>21 (20)</td>
<td>17 (17)</td>
<td>ns</td>
</tr>
<tr>
<td>Macroulbuminuria, n (%)</td>
<td>24 (12)</td>
<td>13 (12.5)</td>
<td>11 (11)</td>
<td>ns</td>
</tr>
<tr>
<td>Retinopathy (panphotocoagulation), n (%)</td>
<td>23 (11)</td>
<td>13 (12.5)</td>
<td>10 (10)</td>
<td>ns</td>
</tr>
<tr>
<td>Abnormal ECG, n (%)</td>
<td>27 (13)</td>
<td>16 (15)</td>
<td>11 (11)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>15 ±9</td>
<td>15 ±10</td>
<td>14 ±9</td>
<td>ns</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>8.4 ±2.3</td>
<td>8.4 ±2.6</td>
<td>8.4 ±2</td>
<td>ns</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>7.7 ±1.6</td>
<td>7.7 ±1.5</td>
<td>7.7 ±1.8</td>
<td>ns</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>89 (44)</td>
<td>46 (44)</td>
<td>43 (43)</td>
<td>ns</td>
</tr>
<tr>
<td>Oral antidiabetic, n (%)</td>
<td>181 (89)</td>
<td>91 (87)</td>
<td>90 (90)</td>
<td>ns</td>
</tr>
<tr>
<td>Beta-blocker, n (%)</td>
<td>40 (20)</td>
<td>15 (14)</td>
<td>25 (25)</td>
<td>ns</td>
</tr>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>90 (44)</td>
<td>47 (45)</td>
<td>43 (43)</td>
<td>ns</td>
</tr>
<tr>
<td>Angiotensin II-receptor antagonist, n (%)</td>
<td>94 (46)</td>
<td>47 (45)</td>
<td>47 (47)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium-channel inhibitor, n (%)</td>
<td>89 (44)</td>
<td>43 (41)</td>
<td>46 (46)</td>
<td>ns</td>
</tr>
<tr>
<td>Antiplatelet therapy, n (%)</td>
<td>105 (51)</td>
<td>51 (49)</td>
<td>54 (54)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns: not significant; LDL/HDL: low-density/high-density lipoprotein; CAD: coronary artery disease; ACE: angiotensin-converting enzyme.
3.2. Prevalence of SMI and detected CAD

SMI was detected by either SPECT or DE in 25 (12%) of the 204 patients included in the present study. The stress test was performed and available in 95 (91%) and 87 (87%) patients by SPECT and DE, respectively (NS).

Of the 104 patients randomized to SPECT, 14 (13%) had SMI. The mean maximum predicted heart rate achieved was 87% (±12). Stress testing involved either exercise (54%), intravenous infusion of dipyridamole (9%) or a combination of both (37%).

Of the 100 patients randomized to DE, 11 (11%) had SMI. Two patients had an intraventricular gradient, one patient had non-sustained ventricular tachycardia and one had transient atrial fibrillation during dobutamine infusion. Five patients did not reach 85% of their maximum predicted heart rate despite receiving the highest dobutamine dose plus atropine. The mean maximum predicted heart rate achieved was 93% with a mean dose of 23 mcg/kg/min of dobutamine plus atropine.

According to univariate analyses, diabetes duration, LDL cholesterol, triglycerides and ECG anomalies were associated with SMI. Multivariate analyses indicated that duration of diabetes was the only independent factor predictive of SMI ($P = 0.02$).

Of the 25 patients with SMI, coronary angiography was refused in one case. In the remaining 24 patients, it demonstrated significant coronary stenosis in nine (five single-vessel, three two-vessel and one three-vessel disease), non-significant lesions in three and no lesions (normal) in 12. The PPV of non-invasive stress testing (SPECT and DE) to detect significant coronary stenosis was 36% (29% and 45% for SPECT and DE, respectively; NS; Table 3). The nine patients with significant stenosis were compared with the 173 remaining patients with neither SMI nor significant coronary stenosis on angiography. Multivariate analyses indicated that duration of diabetes was the only independent factor predictive of significant CAD ($P = 0.05$).

### Table 3

<table>
<thead>
<tr>
<th>Total</th>
<th>SPECT</th>
<th>DE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of randomized patients</td>
<td>204</td>
<td>104</td>
<td>100</td>
</tr>
<tr>
<td>SMI, n (%)</td>
<td>25 (12)</td>
<td>14 (13)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>CAD*, n (%)</td>
<td>9 (4)</td>
<td>4 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>36</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>36 ± 13</td>
<td>36 ± 12</td>
<td>36 ± 14</td>
</tr>
<tr>
<td>Cardiac event during follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death, n (%)</td>
<td>3 (1.5)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>3 (1.5)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cardiac death/MI, n (%)</td>
<td>5 (2.5)</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>6 (3)</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; PCI: percutaneous coronary intervention.

* Defined as > 50% diameter stenosis.

b Of stress test in the diagnosis of CAD with > 50% diameter stenosis.

3.3. Follow-up

Six patients with significant coronary stenosis were treated by coronary angioplasty and drug-eluting stents, and one patient underwent coronary artery bypass graft (CABG) surgery. Long-term clinical follow-up was available for 203 (99.5%) of the 204 study patients, with a mean follow-up time of 36 ± 13 months. The 3-year rate of cardiac death and/or MI was 2.5%, and was similar regardless of the stress test used (Table 3). Two patients died due to non-cardiac causes. Of the six patients initially treated by percutaneous coronary intervention (PCI), five had no persistent ischaemia on stress testing performed 6 to 12 months after PCI (ECG treadmill stress test in four cases, and SPECT in two), and one patient had repeat PCI with a stent. During follow-up, PCI was performed in five other patients—one in the SPECT group and four in the DE group (NS)—three because of acute coronary syndrome and two due to symptomatic myocardial ischaemia. No independent predictive factor of a cardiac event was identified on multivariate analyses, including the presence of either SMI or significant coronary stenosis.

4. Discussion

This was the first randomized study to compare SPECT and DE in the detection of SMI in type 2 diabetic patients at high cardiovascular risk. SPECT and DE accuracy was similar in detecting SMI and CAD. Only 4% of the overall study population had significant CAD detected by angiography. After a 3-year (mean) follow-up, the rate of cardiac death and MI was low (2.5%). Patients had the same long-term prognosis whichever stress test was used.

In diabetic patients, the prevalence of SMI varies across a broad range from 12 to 62% [14–16]. This wide variation could be explained by differences in patient selection and stress tests used. The DIAD study [16] showed a 22% prevalence of SMI in asymptomatic diabetic patients, despite a lower risk profile than the patients in our present study (only 60% fulfilled ACC/ADA criteria). Also, in our study, the prevalence of SMI (14%) in intensively treated high-risk asymptomatic type 2 diabetic patients was in the lower range compared with earlier series using conventional risk-factor care. In the DIAD-2 study [17], a 3-year period of intensive therapy was associated with a decrease in SMI rate. These results emphasize the benefits of intensive therapy of cardiovascular risk factors in patients with type 2 diabetes.

However, the present study failed to demonstrate any difference between SPECT and DE in the detection of SMI and CAD in type 2 diabetic patients. The PPV for detecting a significant coronary stenosis did not differ significantly between SPECT and DE. According to the literature, the PPV for the detection of myocardial ischaemia in symptomatic patients is higher than in asymptomatic patients (Bayes’ theorem). For ethical reasons, angiography was not performed in patients with a negative stress
test. This meant that it was not possible to evaluate the specificity, sensitivity and negative predictive value of SPECT and DE. Nevertheless, as the rate of SMI and patients’ clinical characteristics were identical in the two study groups, it may be assumed that the detection of SMI was not underestimated by either method.

Thus, the optimal test for detecting SMI in diabetic patients remains unclear. Exercise stress testing is recommended as the first line of detection of SMI, but many patients are unable to undergo such testing (due to leg arteritis, obesity, advanced age or neuropathy). Despite the reduced echogenicity in patients with a high body mass index (BMI), DE with tissue harmonic imaging carried out by an experienced operator was as effective as SPECT. In their meta-analysis, Kim et al. [18] found higher rates of specificity (84%) and sensitivity (80%) for DE than for other pharmacological stress testing for diagnosing coronary disease. In the study by Penfornis et al. [19], 56 diabetic patients with at least three risk factors underwent the two tests: SMI prevalence was high (47%), and the PPV was 69% for DE and 75% for SPECT. Thus, the choice of which stress test to use needs to be based on other criteria, such as cost, irradiation, echogenicity and feasibility.

In the present study cohort, the long-term prognosis was good irrespective of which test was used, which suggests that the detection of severe CAD was not underestimated. The rate of cardiovascular events was low (<1% per year), despite the 2.9 further risk factors in addition to age, gender and diabetes. In the literature, the reported rates of cardiac events are usually higher in such a population. Indeed, a 3% annual rate of cardiovascular events was reported by Avogaro et al. [20], and a 40% incidence of CAD was found in the MRFIT study [21]. The annual rate of cardiovascular death was 1.2% in the study by Stamler et al. [22], which included diabetic patients with three associated risk factors, and the Steno-2 study [23] demonstrated that intensive treatment of diabetes and cardiovascular risk factors can reduce cardiovascular mortality in high-risk diabetic type 2 patients with microalbuminuria. In the present study, patients benefited from intensive treatment of cardiovascular risk factors, and the majority had closely followed the recommendations for several years before inclusion. Correction of cardiovascular risk factors in our study and in the intensive arm of the Steno-2 study was similar, with HbA1c values ranging from 7.5–8.0%, while 50% of the patients had systolic blood pressure >130 mmHg, 30% had a diastolic blood pressure >80 mmHg and 86% were taking lipid-lowering therapy [23]. This could partly explain the low rate of patients with severe CAD, despite the selection criteria, and the favourable long-term prognosis. Also, our present results were similar to the 3.5-year rates of MI and cardiac death reported in the standard-therapy group of the ACCORD study (1.3% and 0.3%, respectively) [24].

In the present study, only 3% of patients underwent an initial revascularization, which was similar in both groups; thus, the benefits of revascularization in asymptomatic type 2 diabetic patients with SMI have yet to be demonstrated. The COURAGE study [11] failed to show any benefit of PCI vs intensive medical care in patients with stable CAD and, likewise, the BARI 2D study [6] demonstrated no benefit of PCI over optimal medical therapy in diabetic patients with stable CAD. However, patients in whom revascularization is usually beneficial—such as those with left main stenosis or cardiac failure—were not included in the BARI 2D trial. Also, in the CABG analysis, which involved patients with more severe disease, the rate of 5-year major cardiac events was lower in the revascularization group (22%) than in the medical-therapy group (30%; P<0.01) [6]. In our study, revascularization was performed in only a few patients (3%), mainly those with single-vessel disease, so the low rate of 3-year cardiac events was more likely related to the intensive treatment of cardiovascular risk factors before and during the study than to revascularization.

The benefit of screening diabetic patients to detect SMI and CAD remains controversial. The DIAD study, involving 1123 asymptomatic diabetic patients, failed to demonstrate any benefit with isotope screening for myocardial ischaemia [17]. However, patients in the DIAD study were at low risk: 40% had fewer than two additional risk factors; 1% had >10% defect size in the left ventricle on SPECT; and their annual rate of cardiac death/MI was only 0.6% [17]. Both the SFC/ALFEDIAM and ACC/ADA issued strict guidelines that recommended SMI screening in diabetic patients with peripheral or carotid disease, or two or more other risk factors [3,4]. In the present study, 93% of patients fulfilled these SFC/ALFEDIAM and ACC/ADA guidelines. Despite a mean of 2.9 additional risk factors besides age, gender and diabetes, the annual rate of cardiac death/MI was <1%, whatever the stress test used. In addition, only 3% of our patients underwent revascularization, mainly because of single-vessel disease, which suggests that our inclusion criteria for SMI screening in the setting of intensive care of cardiac risk factors were not sufficiently strong. Neither SMI screening nor revascularization of diabetic patients at low cardiac risk with optimal medical treatment reduces the risk of major cardiac events [6,17]. Our present study confirms a good prognosis for diabetic patients—even those with numerous cardiac risk factors—and does not support the usefulness of systematic SMI screening when these risk factors are being intensively treated. Yet, the diabetic patients in whom SMI screening and revascularization might reduce the risk of cardiac events need to be identified. The selection criteria for SMI screening should be revisited to select those diabetic patients who might be at higher risk, such as those with peripheral arterial disease or nephropathy.

5. Conclusion

Either SPECT or DE can be used in type 2 diabetic patients with the same efficiency to detect SMI. Despite inclusion criteria that were closely related to the current guidelines, diabetic patients whose cardiovascular risk factors are intensively treated have low rates of detected SMI and CAD, and favourable long-term cardiac outcomes. These findings raise the question of the identification of diabetic patients receiving optimal medical therapy for whom SMI screening and revascularization might reduce the risk of cardiac events. In addition, the benefits of the detection and treatment of SMI in such a population need to be confirmed by randomized studies.
Conflict of interest statement

There is no conflict of interest.

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