



The report of male gender and retinopathy status improves the current consensus guidelines for the screening of myocardial ischemia in asymptomatic type 2 diabetic patients

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Abstract *Background and aims:* American Diabetes Association (ADA), French-speaking Societies for diabetes & cardiology (ALFEDIAM-SFC) and Cardiac Radionuclide Imaging (CRI) have proposed guidelines for the screening of silent myocardial ischemia (SMI). The aim of the study was to evaluate their diagnostic values and how to improve them.

Methods and results: 731 consecutive type 2 diabetic patients with ≥ 1 additional risk factor were screened between 1992 and 2006 for SMI by stress myocardial scintigraphy and for silent coronary artery disease (CAD) by coronary angiography. A total of 215 (29.4%) patients had SMI, and 79 of them had CAD. ADA (Odds Ratio 1.7 [95% Confidence Interval: 1.2–2.5]; $p < 0.05$), ALFEDIAM-SFC (OR 1.5 [1.0–2.5], $p < 0.05$) and CRI criteria (OR 2.0 [1.4–2.8], $p < 0.01$) predicted SMI. Considering the presence of male gender and retinopathy added to the prediction of SMI allowed by ADA criteria (c statistic: area under the curve AROC 0.651 [0.605–0.697] versus 0.582 [0.534–0.630]), $p < 0.01$ and ALFEDIAM-SFC criteria (AROC 0.672 [0.620–0.719] versus 0.620 [0.571–0.670], $p < 0.05$). CRI prediction of SMI was improved by considering the presence of macroproteinuria

Abbreviations: ADA, American Diabetes Association; ALFEDIAM-SFC, French Language Association for the Study of Diabetes and Metabolic Diseases (ALFEDIAM), and French Society of Cardiology (SFC: Société Française de Cardiologie); AROC, area under the receiver operating characteristic curve; CAD, coronary artery disease; CRI, Appropriate Use Criteria for Cardiac Radionuclide Imaging; DIAD, Detection of Ischemia in Asymptomatic Diabetics; PCOAD, peripheral or carotid occlusive arterial disease; SMI, silent myocardial ischemia.

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and retinopathy (AROC 0.621 [0.575–0.667] versus 0.594 [0.548–0.641], $p < 0.01$). Severe retinopathy (OR 3.4 [1.2–9.4], $p < 0.05$), smoking habits (OR 2.1 [1.1–4.2], $p < 0.05$) and triglyceride levels (OR 1.3 [1.0–1.6], $p < 0.05$) were independent predictors of CAD in the patients with SMI.

Conclusion: Current guidelines criteria are able to predict SMI but prediction may be improved by considering male gender and the presence of retinopathy. CAD is more frequent in the patients with SMI who are current smokers, have severe retinopathy and higher triglyceride levels.

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Introduction

Type 2 diabetes is associated with a high prevalence of coronary artery disease (CAD) [1–3], with a 2- to 4-fold increase in silent myocardial ischemia (SMI) as compared with the non diabetic population [2,4,5]. SMI has been reported in 7–65% of the diabetic population [6]; it is a strong predictor of future coronary events and premature death [7], with a significant additional value to routine cardiovascular risk assessment [8].

Due to the huge number of diabetic patients, screening for SMI should not be systematic and an indication based on coronary risk stratification has been proposed [1–3]. In this perspective, the American Diabetes Association (ADA) first stated in 1998 that asymptomatic diabetic patients with a normal resting ECG should undergo cardiac testing when peripheral or carotid occlusive arterial disease (PCOAD), or two or more risk factors were present (Table 1) [1]. In 2004, the French Language Association for the Study of Diabetes and Metabolic Diseases (ALFEDIAM) and the French Society of Cardiology (SFC) held their first joint conference that updated previous ALFEDIAM guidelines, by considering diabetes duration [9] and age [10,11] as additional predictive factors [2] (Table 1). Recently however, both ADA [9] and ALFEDIAM-SFC criteria [12] were shown to be unable to accurately predict SMI in a non selected diabetic population. Finally, the 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging issued from a consortium of professional societies (CRI criteria) [13] considered that it was appropriate to screen asymptomatic diabetic patients when they had PCOAD or a 10-year absolute coronary heart disease risk greater than 20% (Table 1) [14]. These screening criteria have not been tested so far.

ALFEDIAM-SFC guidelines stated that patients with SMI should undergo a coronary angiography [2], because SMI prognosis was worse when it was associated with silent CAD, *i.e.* angiography-diagnosed coronary stenosis [7] and because this strategy could detect the patients eligible for coronary revascularization procedure. However, coronary angiography has not been often performed in patients with SMI [9] and little has been shown on the predictive factors of silent CAD in patients with SMI.

The aim of the present study was to investigate in a large series of asymptomatic patients with type 2 diabetes (*i*) the diagnostic value for SMI of the 1998 ADA, the 2004 ALFEDIAM-SFC and the 2009 CRI guidelines criteria; and how to improve them; and (*ii*) the predictive factors of CAD in patients with SMI.

Methods

Participants

The patients were prospectively recruited in the Department of Diabetology of Jean Verdier Hospital (Bondy,

France) between 1992 and 2006. This study was approved by the Ethical Committee of Reims, France. Each enrolled patient gave informed consent in accordance with the European directives. Eligibility criteria included type 2 diabetes, no history of myocardial infarction or angina pectoris, normal 12-lead resting ECG, and the presence of at least one of the following additional cardiovascular risk factors: dyslipidemia (total cholesterol > 6.5 mmol/l and/or LDL-cholesterol $>$

4.1 mmol/l and/or HDL-cholesterol < 0.9 mmol/l and/or triglycerides > 2.3 mmol/l and/or lipid lowering medication), hypertension (blood pressure $> 140/90$ mmHg or anti-hypertensive treatment), smoking, nephropathy (urinary albumin excretion rate > 30 mg/day on at least two measurements and/or creatinine clearance < 60 ml/min), macroproteinuria (urinary protein excretion rate ≥ 0.3 g/24 h) family history of premature CAD (before the age of 60 in first-degree relatives), PCOAD (stenosis measured $\geq 50\%$ by ultrasound examination). Diabetes diagnosis was based on self-report, physician diagnosis, blood tests, and/or hypoglycemic medication use. Exclusion criteria included congenital heart disease or known cardiomyopathy. Diabetic retinopathy was assessed in the previous six months on fundoscopy by an ophthalmologist who was unaware of the results of the cardiovascular investigations. Retinopathy was graded according to the Early Treatment of Diabetic Retinopathy Study severity scale and defined as absent or present, as well as absent, mild/moderate (minimal and moderate nonproliferative retinopathy), and severe (severe nonproliferative or proliferative retinopathy) [15]. The diagnosis of peripheral neuropathy was based on the presence of any two or more of the following: neuropathic symptoms, decreased distal sensation, or decreased or absent ankle reflexes. The 10-year absolute coronary heart disease risk was calculated according to the Framingham equation [14].

Cardiovascular investigations

Screening for SMI

The protocol was previously reported [7,10]. Each patient underwent a thallium 201 myocardial scintigraphy after an ECG stress test, or a pharmacological stress test (dipyridamole injection), or both. The ECG stress test was performed in patients who could exercise on a bicycle ergometer and could be 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 or an abnormal myocardial scintigraphy imaging, *i.e.* defects in at least 3 out of 17 segmental regions, or both.

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