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# Predictors and prognostic impact of silent coronary artery disease in asymptomatic high-risk patients with diabetes mellitus☆

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ABSTRACT

*Aims:* Evaluation of predictors of silent coronary artery disease (SCAD) in high-risk asymptomatic diabetic patients and to evaluate their two-year outcome.
*Methods and results:* Four hundred diabetic patients without prior CAD but at high CAD risk underwent myocardial perfusion scintigraphy (MPS) in this prospective multicentre outcome trial. MPS were abnormal in 22% of patients. Male sex (OR 2.223, 1.152–4.290; p = 0.017), diabetes duration (OR 1.049,1.015–1.085; p = 0·005), peripheral artery disease (OR 2.134, 1·150–3.961; p = 0.016), smoking (OR 2.064, 1.109–3.839; p = 0·022), systolic blood pressure (OR 1.014, 1.00–1.03, p = 0·056), brain natriuretic peptide (OR 1.002, 1.001–1.004, p = 0·005) independently predicted an abnormal MPS: if <2 and >3 predictors were present, 3.2% and 47% patients had an abnormal MPS, respectively (p < 0·001). Two-year major adverse cardiac event rates increased from 2·9% to 14·6%, cardiac death rates from 0·6% to 4·1% in patients with summed stress scores ≤10 and >10%, respectively (each p < 0.045).
*Conclusions:* Male sex, diabetes duration, peripheral artery disease, smoking, elevated systolic blood pressure and increased brain-natriuretic peptides independently predicted SCAD. In presence of >3 predictors, almost 50% of patients had an abnormal MPS. They may benefit from screening by MPS since the extent of the MPS abnormality discriminated clearly between a favourable compared to a bad 2-year outcome. However, even highest risk patients without objective evidence of CAD had a benign prognosis without need for specific evaluation or therapy.
Trial Registration Number: ISRCTN87953632.


## 1. Introduction

Diabetes mellitus is an important risk factor for coronary artery disease (CAD) and it has been shown that silent CAD affects 20–35% of patients with diabetes [1,2]. Still, the American Diabetes Association does not recommend routine CAD screening [3], mainly based on the Detection of Silent myocardial Ischemia in Asymptomatic Diabetic Subjects trial (DIAD), which implied that general CAD screening does not improve outcome as long as cardiovascular risk factors are treated [3]. In contrast, European guidelines challenged this position arguing that there are high risk patients who may benefit from specific treatment if they can be identified by appropriate screening [4]. However, high risk clinical characteristics of such patients need to be better defined.

The present study aimed to 1) evaluate clinical characteristics that may help to identify patients with a high probability of silent CAD documented by an abnormal stress MPS in asymptomatic diabetic patients without any manifestation of CAD, but at high coronary risk according to the American Diabetes Association [5] and 2) to assess the prognostic value of this finding in such patients on 2-year outcome.

*Abbreviation list:* CAD, Coronary artery disease; BARDOT, Basel, Asymptomatic high-Risk Diabetics' Outcome Trial; MPS, Myocardial Perfusion scintigraphy; SSS, Summed Stress Score; SRS, Summed Rest Score; SDS, Summed Difference Score; BNP, Brain Natriuretic Peptide.

☆ The authors report no relationships that could be construed as a conflict of interest.

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## 2. Methods

### 2.1. Study design

The present study is an a priori planned analysis as central part of the Basel Asymptomatic high Risk Diabetics' Outcome Trial (BARDOT) of which the protocol and amendment have been published previously [2]. BARDOT was a prospective multicentre outcome trial in three centres in Germany (district hospital of Schopfheim, Germany; district hospital of Lörrach, Germany) and Switzerland (University Hospital of Basel, Switzerland). Study patients underwent clinical visits and rest/stress myocardial perfusion single photon emission computed tomography (MPS) at baseline and after two years of follow-up as described previously [2]. Independent clinical predictors of abnormal baseline MPS were evaluated. BARDOT was approved by the ethics committees of all participating centres and all patients gave written informed consent.

### 2.2. Participants

For inclusion in the BARDOT trial, study patients had to have type-2 diabetes and neither history nor symptoms of CAD i.e. they were free from CAD manifestations (no typical or atypical angina, no history of myocardial infarction or revascularization), i.e. they were "asymptomatic". They had to be at high risk of CAD documented by end-organ damage (peripheral or carotid occlusive disease, retinopathy, microalbuminuria, autonomic cardiac neuropathy as measured by Ewing et al. [6]), *or* by the composite of age >55 years, diabetes duration >5 years, and two cardiac risk factors (smoking, hypertension, hypercholesterolemia, or positive family history of CAD) in addition to diabetes.

Exclusion criteria of the study were: age above 75 years, severe illness with a life expectancy of <3 years, known prior CAD, or shortness of breath (NYHA IV).

Between June 2002 and December 2010, 400 out of 2018 patients screened were eligible for this study and consented. The enrolment period was longer than expected because it was more difficult than anticipated to recruit asymptomatic diabetic patients willing to participate in this long-term study with repeated testing.

### 2.3. Procedures

Clinical examinations, standard laboratory testing and follow-up visits after one and two years were performed in the outpatient clinics of each centre. Rest/stress gated MPS studies were performed for all patients at the core laboratories of the University Hospital Basel following a standard protocol as described before [2,7–9]. In short, a rest-stress (99mTechnetium sestamibi, 400 MBq/800 MBq) protocol with symptom-limited exercise or adenosine stress and electrocardiographic monitoring was used. Images were scored using a 17-segment model with a five-point scale from 0 = normal to 4 = no uptake [10]. Summed scores (stress, rest and difference scores) were calculated summarizing the perfusion scores of the 17 segments and also converted into % myocardium abnormal. Summed stress scores (SSS) represent the overall perfusion abnormality of the scan, whereas summed difference scores (SDS) represent the severity and extent of ischemia and summed rest scores (SRS) perfusion abnormality at rest. The following categories for SSS, SDS, and SRS were then derived to provide information regarding baseline and follow-up perfusion defects: 0% myocardium, 0.1–4.9%, 5–9.9%, and 10% or higher. All patients with abnormal MPS results were treated with aspirin, a statin and a betablocker while therapy with ACE- and ARB- inhibitors was advised [2].

### 2.4. Definitions and endpoints

A perfusion scan was considered abnormal with an SSS ≥4, consistent with ≥5% of the myocardium affected. Ischaemia was defined as reversible defect with an SDS of ≥2 (≥3% myocardium ischemic) and scar with at least one non-reversible segment [11,12]. Based on these criteria, an abnormal MPS result was defined as evidence of CAD and a normal MPS result as absence of CAD.

Cardiac death was defined as any death not clearly due to extra cardiac reasons, myocardial infarction (MI) according to current definitions [13] and revascularization as symptom-driven revascularization (i.e. revascularizations necessary in patients who became symptomatic and remained so despite medical therapy). Major adverse cardiac events (MACE) were cardiac death, MI or symptom-driven revascularizations.

An independent Critical Events Committee adjudicated all clinical events blinded to baseline MPS results and study group assignment.

### 2.5. Statistical analysis

Baseline characteristics of patients with versus without evidence of silent CAD and follow-up characteristics with normal MPS at baseline were compared by independent t- or Mann-Whitney *U* tests (as appropriate) for continuous variables and chi-square tests for binary variables.

Independent predictors of an abnormal MPS were analysed by a binary logistic regression analysis (with binomial error) to estimate odds ratios (OR) with 95% confidence intervals.

With respect to the number of independent variables predicting an abnormal MPS the following continuous variables were divided into 2 categories. If the value was above the defined threshold the predictor was considered to be present: diabetes duration (≥10 years), B-type natriuretic peptide (BNP > 50.3 pg/l [cut-off of the used assay]) and systolic blood pressure (≥140 mm Hg).

Statistical analyses were performed using the IBM SPSS statistics (Version 22).

### 2.6. Role of the funding source

None of the sponsors mentioned above had any influence on the design and conduct of the study, interpretation of the data, nor the decision to submit the manuscript to publication.

## 3. Results

### 3.1. Prevalence of silent CAD at baseline

Study patients had an age range from 35 to 75 years, two thirds were men with an average diabetes history of 11 ± 8 years. The mean scintigraphically determined left ventricular ejection fraction was 58 ± 11%. Overall, 50% of all patients were on insulin and 80% on oral glucose lowering agents. The majority of patients was on cardioactive drugs, particularly antihypertensives, 53% were on antiplatelet therapy and 57% on lipid lowering medications. Baseline MPS was normal in 313 and abnormal in 87 patients (22%), i.e. 22% of patients were considered to have silent CAD.

Baseline characteristics of patients with versus without evidence of CAD are summarized in Table 1. Compared to patients with a normal

**Table 1**
Baseline characteristics of patients with normal versus abnormal MPS Variable.

| | Patients with normal MPS (n = 313) | Patients with abnormal MPS (n = 87) | p-Value[b] |
|---|---|---|---|
| Age (years)[a] | 63 ± 8 | 65 ± 7 | 0.01 |
| Male sex (%) | 65 | 84 | <0.001 |
| Diabetes duration (years)[a] | 10 ± 7 | 13 ± 9 | 0.0019 |
| BMI (kg/m$^2$)[a] End-organ damage: | 31 ± 6 | 31 ± 6 | 0.92 |
| - Retinopathy (%) | 22 | 29 | 0.22 |
| - Polyneuropathy (%) | 46 | 58 | 0.06 |
| - Nephropathy (%) | 44 | 55 | 0.08 |
| - Autonomic neuropathy (%) | 42 | 60 | 0.0075 |
| - Peripheral artery disease (%) | 11 | 29 | <0.001 |
| - Stroke/TIA (%) | 9 | 9 | 1.00 |
| Patients with ≥1 of listed end-organ damages | 86 | 92 | 0.19 |
| Smoking (%) | 18 | 32 | 0.0047 |
| Shortness of breath (NYHA I–III) (%) | 45 | 53 | 0.24 |
| Resting heart rate (bpm)[a] | 74 ± 11 | 77 ± 13 | 0.06 |
| Systolic blood pressure (mm Hg)[a] | 137 ± 19 | 141 ± 17 | 0.02 |
| HbA1c (%)[a] | 7·3 ± 1·2 | 7·4 ± 1·3 | 0.39 |
| Microalbuminuria (%) | 44 | 54 | 0.14 |
| Creatinine (μmol/l)[a] | 75 ± 23 | 85 ± 25 | <0.001 |
| Total cholesterol (mmol/l)[a] | 4·7 ± 1·0 | 4·5 ± 1·1 | 0.27 |
| LDL cholesterol (mmol/l)[a] | 2·5 ± 0·9 | 2·4 ± 1·0 | 0.19 |
| BNP (ng/l) median | 34 | 49 | 0.02 |
| Antiplatelet drugs (%) | 50 | 63 | 0.03 |
| Oral anticoagulants (%) | 4 | 6 | 0.83 |
| Beta blocker (%) | 31 | 36 | 0.49 |
| Calcium antagonist (%) | 23 | 33 | 0.07 |
| Statins (%) | 55 | 66 | 0.10 |
| ACE-I/ARB (%) | 74 | 84 | 0.10 |
| Diuretics (%) | 46 | 59 | 0.05 |
| Oral glucose lowering therapy (%) | 79 | 84 | 0.38 |
| Insulin (%) | 50 | 51 | 1.00 |
| ECG q-waves (%) | 5·3 | 3·8 | 0.22 |
| Ergometry: exercise/ pharmacologic/combined (%) | 81/4/15 | 57/15/28 | <0.001 |
| Symptoms during ergometry (%) | 12 | 16 | 0.48 |
| ECG changes during ergometry (%) | 5 | 26 | <0.001 |
| SSS/% myocardium (median) | 0 | 8/11·8 | <0.001 |
| SDS/% myocardium ischemic (median) | 0 | 3/4·4 | <0.001 |
| Left ventricular ejection fraction (%)[a] | 60 ± 9 | 51 ± 14 | <0.001 |

Abbreviations: MPS = myocardial perfusion SPECT; ACE/ARB = angiotensin-enzyme inhibitor/angiotensin-receptor blocker; BMI = body mass index; bpm = beats per minute; ECG = electrocardiogram; HDL = high-density lipoprotein; HbA1c = Hemoglobin A1c; NYHA = New York Heart Association; SD = standard deviation; TIA = transient ischemic attack.

[a] Plus–minus values are means ± SD.

[b] p-Values were calculated with the use of a Mann-Whitney test for quantitative variables and a chi-square test for qualitative variables.