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Progression to Overt or Silent CAD in Asymptomatic Patients With Diabetes Mellitus at High Coronary Risk

Main Findings of the Prospective Multicenter BARDOT Trial With a Pilot Randomized Treatment Substudy

Michael J. Zellweger, MD,* Michael Maraun, MD,† Hans H. Osterhues, MD,‡ Ulrich Keller, MD,§ Jan Müller-Brand, MD,‖ Raban Jeger, MD,* Otmar Pfister, MD,* Thilo Burkard, MD,* Friedrich Eckstein, MD,¶ Stefanie von Felten, PhD,# Stefan Osswald, MD,* Matthias Pfisterer, MD*

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate prevalence, progression, treatment, and outcome of silent coronary artery disease (CAD) in asymptomatic patients with diabetes (DM) at high coronary risk.

BACKGROUND Despite the close association of diabetes and CAD, general CAD screening in asymptomatic patients with DM is discouraged even though outcome data in patients at high coronary risk are lacking.

METHODS Prospective multicenter outcome study—with a pilot randomized treatment substudy. The study comprised 400 asymptomatic patients with DM (type 2) without history or symptoms of CAD at high CAD risk. They underwent clinical evaluation and myocardial perfusion single-photon emission computed tomography (MPS) at baseline and after 2 years. Patients with normal MPS received usual care; those with abnormal MPS received medical or combined invasive and medical management.

RESULTS An abnormal MPS was found in 87 of 400 patients (22%). In patients with normal MPS, MACE occurred in 2.9% and ischemia or new scar in 3.2%. Patients with abnormal MPS had more MACE (9.8%; hazard ratio: 3.44; 95% confidence interval [CI]: 1.32 to 8.95; $p = 0.011$) and ischemia or new scar (34.2%; odds ratio: 15.91; 95% CI: 7.24 to 38.03; $p < 0.001$) despite therapy, resulting in "overt or silent CAD progression" of 35.6% versus 4.6% (odds ratio: 11.53; 95% CI: 5.63 to 24.70; $p < 0.001$). Patients with abnormal MPS randomized to medical versus invasive-medical strategies had similar event rates ($p = 0.215$), but more ischemic or new scar findings (54.3% vs. 15.8%; $p < 0.001$).

CONCLUSIONS High-risk asymptomatic patients with DM and normal MPS (78%) have a low rate of first manifestations of CAD. Patients with abnormal MPS at baseline (22%) have a 7-fold higher rate of progression to "overt or silent CAD," despite therapy. Randomized patients' outcomes suggest that a combined invasive and medical strategy for silent CAD may reduce scintigraphic but not symptomatic CAD progression versus medical therapy alone. (Trial of Invasive versus Medical therapy of Early coronary artery disease in Diabetes Mellitus ISRCTN87953632) (J Am Coll Cardiol Img 2014;7:1001–10) © 2014 by the American College of Cardiology Foundation.

From the *Department of Cardiology, University Hospital, University of Basel, Basel, Switzerland; †District Hospital, Schopfheim, Germany; ‡District Hospital, Lörrach, Germany; §Division of Endocrinology, University Hospital, University of Basel, Basel, Switzerland; ‖Division of Nuclear Medicine, University Hospital, University of Basel, Basel, Switzerland; ¶Department of Cardiac Surgery, University Hospital, University of Basel, Basel, Switzerland; and the #Clinical Trial Unit, University Hospital, University of Basel, Basel, Switzerland. The present study was supported by the Swiss National Foundation for Research (Nr 3200B0-100620); the Swiss Heart Foundation, Bern, the Foundation for Cardiovascular Research, Basel; the Foundation of the Diabetes Association of Basel; Roche Switzerland; Pfizer Switzerland; Takeda Switzerland; and Heider & Co., Switzerland. None of the sponsors mentioned above had any influence on the design and conduct of the study, interpretation of the data, or the decision to submit the manuscript to publication. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

MACE = major adverse cardiac events

MPS = myocardial perfusion single-photon emission computed tomography

Despite the known association between diabetes and coronary artery disease (CAD), the prevalence of silent CAD in patients with diabetes is low (1–3), so that screening for silent ischemia is not advised (3–5). This recommendation was adopted for asymptomatic patients with diabetes by the American Diabetes Association (6,7), but recent guidelines stated that "the characteristics of the patients who should be screened for CAD need to be better defined. Further evidence is needed to support screening for silent myocardial ischemia in high-risk patients with diabetes mellitus" (8). The present study aimed to provide such evidence studying the 2-year outcome of patients with diabetes without history and symptoms of CAD, but at high coronary risk according to the American Diabetes Association (6). The specific aims of the present prospective multicenter diagnostic and outcome study were to answer the following questions: what is the prevalence of myocardial ischemia in high-risk asymptomatic patients with diabetes? What is the rate of a first manifestation of CAD in patients without evidence of CAD at baseline? What is the rate of progression to major adverse cardiac events (MACE) or to persistent, treatment-refractory silent CAD in patients with abnormal myocardial perfusion single-photon emission computed tomography (MPS)? Because antiischemic treatment could not be withheld to patients with abnormal MPS for ethical reasons, a fourth question was added in a pilot-type randomized substudy: What therapeutic options might be considered to improve outcome?

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The present report presents the main findings of this study, BARDOT (Basel Asymptomatic high-Risk Diabetics' Outcome Trial).

METHODS

PATIENTS. Study patients had type 2 diabetes and neither history nor symptoms of CAD, that is, they were free from CAD manifestations or "asymptomatic." They were 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. [9]) or by the composite of age older than 55 years, diabetes duration longer than 5 years, and 2 cardiac risk factors (smoking, hypertension, hypercholesterolemia, or positive family history of CAD) in addition to diabetes. Patients older than 75 years, with a life expectancy of less than 3 years, or shortness of breath New York Heart Association functional class IV were excluded. Patients were recruited from the diabetic outpatient clinics of the University Hospital Basel, Switzerland, the District Hospitals of Lörrach and Schopfheim, Germany, and from diabetic practices. During 6 study years (enrollment, June 2004 to December 2010), participating clinics screened 2,028 patients (**Figure 1**); 18% of all screened or 41% of eligible patients formed the study population.

DESIGN. Study patients underwent clinical visits and rest and stress MPS at baseline and after 2 years (**Figure 1**). If baseline MPS was normal, patients were followed without specific CAD therapy. Patients with abnormal MPS findings were randomly assigned 1:1 to a medical or medical and invasive anti-ischemic strategy. The medical strategy included risk factor counseling, aspirin 100 mg/day, atorvastatin 40 mg/day, and carvedilol 50 mg/day, and angiotensin-converting enzyme inhibitors were recommended. Patients following the medical and invasive strategy underwent coronary angiography and revascularization if feasible (percutaneous coronary intervention with drug-eluting stent[s] in patients with 1- or 2-vessel disease, bypass surgery in multivessel disease, based on decision making in the Heart Team) in addition to the same medical management as medical patients. It was expected that some patients might refuse revascularization in view of their lack of symptoms and that in about 20% revascularization would not be feasible because of an unfavorable coronary anatomy (distal lesions, diffuse or microvascular disease). By intention-to-treat, these patients were analyzed in the invasive strategy group; however, an "on treatment" analysis was planned a priori.

The study protocol and amendment (Online Appendix) were approved by the ethics committee of all participating centers, and all patients gave written informed consent.

PROCEDURES AND RANDOMIZATION. Rest- and stress-gated MPS studies were performed at the core laboratories of the University Hospital Basel following a standard protocol as described before (10–12). In short, a rest and stress (99m technetium 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 5-point scale from 0 = normal to 4 = no uptake (13). Summed scores (stress, rest, and difference scores) were calculated, summarizing the perfusion scores of the 17 segments, and also converted into percentage of myocardium considered abnormal or ischemic.

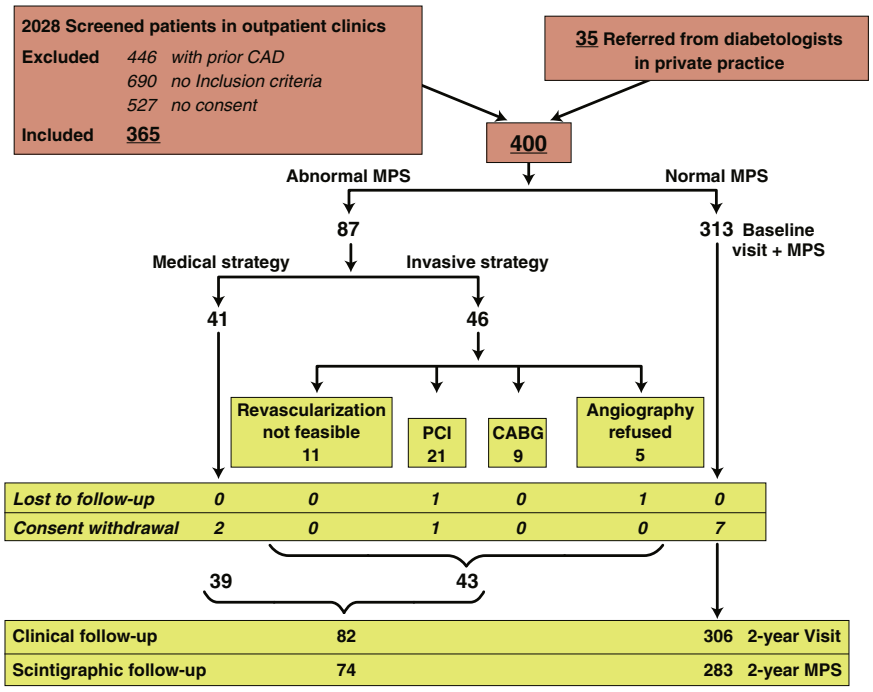

FIGURE 1 Patient Population

Flowchart of the study population and the follow-up after 2 years. CABG = coronary artery bypass grafting; CAD = coronary artery disease; MPS = myocardial perfusion single-photon emission computed tomography; PCI = percutaneous coronary intervention.

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% to 4.9%, 5.0% to 9.9%, and 10.0% or higher.

Coronary angiographies and angioplasties followed standard techniques in Basel and Lörrach, and bypass surgeries were performed in Basel, and one each in Bad Krozingen and Freiburg, Germany. Randomization was performed centrally for each center with sealed envelopes in a sequentially numbered container. The random allocation sequence was generated by a computer. Therapeutic strategies could not be blinded. Follow-up was planned for 2 years ± 3 months.

DEFINITIONS AND ENDPOINTS. Because CAD progression may manifest as symptomatic events or as silent new perfusion defects not present at baseline, the protocol defined 2 components of the primary endpoint "CAD progression": 1) "symptomatic" CAD progression, that is, major adverse cardiac events (MACE: cardiac death, myocardial infarction [MI], and symptom-driven revascularization); and 2) "scintigraphic" CAD progression, that is, myocardial ischemia or new scar in the 2-year MPS compared with baseline (in patients with abnormal MPS, ischemia refractory to intensified therapy was also considered "progression"). In view of the statistical difficulty to accommodate 2 different primary endpoints in one analysis, particularly if only 1 is time-sensitive, and due to some patients refusing repeat MPS, we chose MACE to be the primary endpoint and labeled the scintigraphic endpoint "main" secondary endpoint. The combination of MACE and this main scintigraphic endpoint was defined as "overt or silent CAD progression" to depict the full spectrum of progression to "overt or silent CAD" (Online Appendix, Amendment section).

Cardiac death was defined as any death not clearly attributable to extracardiac reasons, MI according to current definitions (14), and revascularization as late symptom-driven revascularization (i.e., revascularizations necessary in patients who became symptomatic and remained so despite medical therapy). A perfusion scan was considered abnormal with an SSS of 4 or greater, consistent with at least 5% of the myocardium affected. Ischemia was defined as

reversible defect with an SDS of 2 or greater (≥3% myocardium ischemic), and scar as at least one nonreversible segment (15,16). New scar at follow-up was valued as important as ischemia because it indicates intercurrent silent MI. Based on these criteria, an abnormal MPS result represented evidence of CAD, and a normal MPS result as absence of CAD. An independent Critical Events Committee (R.J., O.P., and T.B.) adjudicated all clinical events blinded to baseline scintigraphic results and study group assignment.

STATISTICAL ANALYSIS. Baseline characteristics of patients with versus without evidence of silent CAD and of patients with abnormal MPS randomly assigned to invasive versus medical treatment strategies were compared by Mann-Whitney *U* tests for continuous variables and chi-square tests for binary variables.

MACE and their components were compared using Cox proportional hazard models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) and by Kaplan-Meier curves. Scintigraphic results (ischemia or new scar) and overt or silent CAD progression were analyzed by generalized linear models (with binomial error) to estimate odds ratios (OR) with 95% CI.

The main analysis for the randomized pilot treatment study part was intention-to-treat. A sensitivity analysis was performed for the primary endpoint, assuming an event for all patients with a missing primary endpoint. Event rates were compared by a generalized linear model because only events but not event dates were imputed. In addition, an "on-treatment" analysis was performed to account for patients in the invasive treatment group who were not revascularized.

Regarding sample size, please see the Online Appendix (dedicated paragraph and study protocol). All statistical analyses were performed by S. vonFelten who was not involved in the conception or conduct of the trial, using the statistical software package R version 2.15.1, R Core Team, 2012 (R Foundation, Vienna, Austria).

RESULTS

PREVALENCE OF SILENT CAD AT BASELINE. Baseline MPS was normal in 313 and abnormal in 87 patients, that is, 22% (95% CI: 18% to 26%) had abnormal MPS. Baseline characteristics of these 2 groups are summarized in **Table 1**. Patients with abnormal MPS were older, more frequently male, and smokers, and had peripheral vascular disease, autonomic cardiac neuropathy, and longer histories of diabetes with higher systolic blood pressures and higher creatinine and B-type natriuretic peptide values. Overall, 50% of all patients were taking insulin, and 80% were taking oral glucose-lowering agents. The majority of patients were taking cardioactive drugs, particularly antihypertensive agents; 53% were taking antiplatelet therapy, and 57% were taking lipid-lowering medications.

CAD PROGRESSION IN PATIENTS WITH A NORMAL VERSUS ABNORMAL MPS AT BASELINE. The final follow-up performed after 743 ± 77 days (median 732 days) was complete in 388 of 400 patients (97%); 10 withdrew consent because of the state of their illness (all still alive) and 2 were lost to follow-up (**Figure 1**). In addition, 31 patients had no follow-up MPS: 7 had died, 10 had severe comorbid disease, and 14 refused, leaving 357 of 400 patients (89%) with 2 repeat MPS studies.

The evolution of perfusion abnormalities in the whole patient population, in patients with normal MPS, and in patients with abnormal MPS is summarized in **Table 2**.

Patients with normal MPS had 2-year rates of MACE of 2.9%, of cardiac death of 0.7%, and of new ischemia or new scar of 3.2%, resulting in "overt or silent CAD progression" of 4.6% (**Table 3**). Thus, progression to symptomatic or new silent CAD in patients with normal MPS was only 2.3%/year and cardiac mortality was 0.35%/year. In contrast, the hazard to suffer a MACE was more than 3 times higher in patients with an abnormal MPS at baseline (irrespective of treatment) than in patients with a normal MPS (**Table 3**, **Figure 2**): HR: 3.44; 95% CI: 1.32 to 8.95; $p = 0.011$. In addition, the probability of an ischemic or new scar finding was also higher in patients with an abnormal MPS: OR: 15.91; 95% CI: 7.24 to 38.03; $p < 0.001$. Accordingly, "overt or silent CAD progression" was 7-fold higher in patients with a normal versus an abnormal MPS (35.6% vs. 4.6%), documenting the screening efficacy of MPS in these patients.

INFLUENCE OF TREATMENT ON CAD PROGRESSION. Baseline characteristics of the 87 patients with abnormal MPS who were randomly assigned to medical and invasive or medical strategies were similar in both treatment arms, indicating balanced randomization (Online Table 1). Patients with abnormal MPS were treated intensely (**Table 4**), which led to marked reductions in total and LDL-cholesterol, whereas glucose-lowering therapy and hemoglobin A1c values remained unchanged. Of 46 patients undergoing invasive strategy, 5 refused coronary angiography and 11 had a coronary anatomy unsuitable for revascularization (9 with no localized CAD, 2 with

small-vessel CAD) such that only 65% of all patients in the invasive treatment group were revascularized, 19 by percutaneous coronary intervention and 9 by bypass surgery.

By intention-to-treat, medical and invasive treatment and medical strategy patients did not differ significantly in symptomatic CAD progression, despite a considerable difference in the hazard of MACE (HR: 0.36; 95% CI: 0.07 to 1.81; p = 0.215) (Online Figure 1). The sensitivity analysis did not change the overall result (OR: 0.50; 95% CI: 0.14 to 1.65; p = 0.265). However, scintigraphic CAD progression was lower in invasively than in only medically managed patients (OR: 0.16; 95% CI: 0.05 to 0.45; p < 0.001) (Table 5). This resulted in a significantly lower "overt or silent CAD progression" in invasively managed patients (OR: 0.14; 95% CI: 0.04 to 0.40; p < 0.001) (Figure 3). Note that no MACE occurred in revascularized patients (1 of 2 patients who died later had no localized CAD to be revascularized and 1 had refused coronary angiography). Furthermore, scintigraphic results normalized in 32 of 38 revascularized patients compared with only 16 of 35 patients following the medical strategy (84% vs. 46%; p < 0.001).

TABLE 1 Baseline Characteristics of Patients With Normal Versus Abnormal MPS

	Patients With Normal MPS (n = 313)	Patients With Abnormal MPS (n = 87)	p Value*
Age, yrs	63 ± 8	65 ± 7	0.01
Male	65	84	<0.001
Diabetes duration, yrs	10 ± 7	13 ± 9	0.0019
BMI, kg/m^2	31 ± 6	31 ± 6	0.92
End-organ damage			
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	<0.0001
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 functional class I–III)	45	53	0.24
Resting heart rate, beats/min	74 ± 11	77 ± 13	0.06
Systolic blood pressure, mm Hg	137 ± 19	141 ± 17	0.02
HbA1c	7.3 ± 1.2	7.4 ± 1.3	0.39
Microalbuminuria	44	54	0.14
Creatinine, μmol/l	75 ± 23	85 ± 25	<0.001
Total cholesterol, mmol/l	4.7 ± 1.0	4.5 ± 1.1	0.27
LDL cholesterol, mmol/l	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	<0.0001
Symptoms during ergometry	12	16	0.48
ECG changes during ergometry	5	26	<0.0001
SSS/% myocardium, median	0	8/11.8	<0.0001
SDS/% myocardium ischemic, median	0	3/4.4	<0.0001
Left ventricular ejection fraction, %	60 ± 9	51 ± 14	<0.001

Values are mean ± SD or %. *p values were calculated with the use of a Mann-Whitney *U* test for quantitative variables and a chi-square test for qualitative variables.

ACE-I/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; ECG = electrocardiogram; HDL = high-density lipoprotein; HbA1c = hemoglobin A1c; MPS = myocardial perfusion single-photon emission computed tomography; NYHA = New York Heart Association; SDS = summed difference score; SSS = summed stress score; TIA = transient ischemic attack.

DISCUSSION

The BARDOT trial in asymptomatic patients with diabetes showed that within 2 years, fewer than 1 in 20 patients with normal MPS developed first manifestations of CAD despite high-risk features. They made up 78% of all patients tested. In contrast, 1 of 3 similar patients with abnormal MPS either experienced a major cardiac event or had persistent ischemia refractory to intense therapy. This outcome difference was significant for symptomatic and scintigraphic manifestations of CAD, separately. Thus, ischemia testing in patients with diabetes at high coronary risk separates patients with CAD progression from those with a more benign course. These results challenge the recommendation based on the DIAD (Detection of Ischemia in Asymptomatic Diabetes) study findings (3–5) not to screen asymptomatic patients with diabetes. They provide trial evidence, so far lacking, to the new European "class IIb" recommendations to perform ischemia testing in high-risk asymptomatic patients with diabetes (8). Even though the optimal therapy is still open to question, the small randomized treatment pilot substudy presented here suggests that subclinical progression to silent CAD may be reduced and the resolution of silent perfusion defects greater by invasive and medical treatment compared with medical management only, indicating that an appropriately sized randomized trial for clinical endpoints is warranted (a limitation of the present study is that only 65% of patients randomly assigned to the invasive strategy were revascularized).

Novel aspects and strengths of the present study are the following: only asymptomatic patients at high risk of CAD based on readily available clinical parameters were selected. They had clinical and MPS

TABLE 2 Evolution of Perfusion Defects in the Whole Patient Population, in Patients With Normal and Abnormal Baseline MPS*

	All Patients		Patients With Normal MPS at Baseline		Patients With Abnormal MPS at Baseline Medical Therapy		Patients With Abnormal MPS at Baseline Revascularization Therapy	
Perfusion Defects	Baseline (n = 400)	Follow-Up (n = 357)	Baseline (n = 313)	Follow-Up (n = 283)	Baseline (n = 41)	Follow-Up (n = 36)	Baseline (n = 46)	Follow-Up (n = 38)
SSS, % myocardium								
0.0	71	75	91	90	2	14	0	24
0.1–4.9	8	10	9	8	2	11	4	21
5.0–9.9	9	8	0	1	37	28	41	45
≥10.0	12	7	0	1	59	47	55	10
SDS, % myocardium								
0.0	84	90	100	96	22	44	28	90
0.1–4.9	8	5	0	3	39	19	35	8
5.0–9.9	7	3	0	0	32	25	33	3
≥10.0	1	2	0	1	7	11	4	0
SRS, % myocardium								
0.0	74	75	91	88	15	22	15	26
0.1–4.9	13	12	9	10	29	17	22	21
5.0–9.9	7	10	0	2	24	42	37	42
≥10.0	6	3	0	0	32	19	26	11

Values are %. *In patients with abnormal baseline MPS, results are reported separately for patients who underwent medical or medical plus revascularization therapy.
MPS = myocardial perfusion single-photon emission computed tomography; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

examinations not only at baseline but again after 2 years, a period long enough to detect relevant CAD progression. Manifestations of CAD were not restricted to cardiac events, but included newly detected ischemia and new scar, indicating in the absence of symptoms, silent CAD. In addition, CAD progression was diagnosed based on MACE rates and MPS findings but not on coronary angiography to which asymptomatic patients would hardly agree. Then, there was a smaller than anticipated patient number in the treatment part because the prevalence of silent ischemia was lower than expected despite high-risk features, resulting in a low power of the pilot substudy. However, the only 2 randomized trials evaluating the treatment of silent CAD were small "pilot-type" trials (17,18), too. Unfortunately, but not unexpectedly, only 65% of patients randomly assigned to the invasive strategy were revascularized; the remainder refused angiography for lack of symptoms or had an unsuitable anatomy for revascularization. In the only other prospective treatment comparison of patients with chronic CAD not relying a priori on a coronary anatomy suitable for revascularization (19), a similar rate of patients could not be revascularized, despite refractory symptoms. This fact called for an on-treatment analysis in the present study which demonstrated that MACE tended to be lower in revascularized patients than in patients treated medically ($p = 0.064$). This also holds true by protocol analysis with respect to severely abnormal perfusion abnormalities. At baseline, patients treated medically and medically plus revascularization had

TABLE 3 Two-Year Outcome Events in Patients With Normal Versus Abnormal MPS

	All	Patients With Normal MPS (n = 306)	Patients With Abnormal MPS (n = 82)	HR/OR* (95% CI)	p Value*
Patients with MACE	17 (4.4)	9 (2.9)	8 (9.8)	3.44 (1.32–8.95)	0.011
Cardiac death	4 (1.0)	2 (0.7)	2 (2.4)	3.77 (0.53–26.77)	0.184
Myocardial infarction	6 (1.6)	3 (1.0)	3 (3.7)	3.77 (0.76–18.69)	0.104
Revascularization	12 (3.1)	6 (2.0)	6 (7.3)	3.90 (1.25–12.16)	0.019
Scintigraphic ischemia or new scar†	34 (9.5)	9 (3.2)	25 (34.2)	15.91 (7.24–38.03)	<0.001
Patients with "overt or silent CAD progression"†	39 (10.9)	13 (4.6)	26 (35.6)	11.53 (5.63–24.70)	<0.001

Values are n (%). *p values from Cox proportional-hazards survival model (HR and 95% CI) except for scintigraphic ischemia or new scar and "overt or silent CAD progression" (OR and 95% CI from generalized linear model). †n = 284 and n = 73 for patients with normal and abnormal MPS, respectively.
CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; MPS = myocardial perfusion single-photon emission computed tomography; OR = odds ratio.

severely abnormal MPS results in 59% and 55% of patients, respectively (p = 0.69). At follow-up, significantly fewer patients with revascularization had a severely abnormal MPS than patients only treated medically, 10% and 47%, respectively (p < 0.001).

In published reports, the prevalence of silent CAD varied widely, from <10% to >50% (20–22). The DIAD study found 22% of patients had abnormal tests and concluded that cardiac event rates were low and not reduced by screening (2,3). Present results may seem to contradict these findings and those from a French study (1); however, these studies compared screening with no screening, taking into account that up to 20% of unscreened patients with silent CAD remained undetected, minimizing outcome differences. In contrast, the present study tested all patients comparing those with versus without MPS evidence of CAD. Then, BARDOT patients were selected for high coronary risk: compared with DIAD patients, BARDOT patients were on average 2 years older, had 2.4 years longer diabetes duration, higher hemoglobin A1c values, end-organ damage more frequently (altogether in nearly 90% of patients), and higher rates of standard CAD risk factors, and were more often on insulin therapy (50% vs. 10% in DIAD). These data document the higher risk of BARDOT patients. In addition, only 6% of DIAD patients had perfusion defects of at least 5% of the myocardium as required in all BARDOT patients. Finally, outcome measures of DIAD were restricted to cardiac death or MI, whereas in the current study overt or silent CAD progression was assessed and patients with scintigraphic evidence of CAD had protocol-mandated intense therapy, in contrast to DIAD. Therefore, the present results and those of DIAD are not contradictory but rather complementary: although general screening of asymptomatic patients with diabetes has a low yield as documented by DIAD, it may be of prognostic value in asymptomatic patients with diabetes at high coronary risk as shown in this study.

Furthermore, the present analysis shows that first manifestations of CAD occurred at an annual rate of only 2.3%, which confirms the "warranty period" of a normal scintigram of 2 to 3 years postulated on the basis of retrospective data (23). It suggests that repeat screening tests should not be performed within 4 to 5 years if their yield should be a 10% event prediction. Only 1% of patients with a normal MPS at baseline developed a severely abnormal MPS during the period of 2 years (Table 2).

Despite its low power, results of the randomized treatment pilot substudy added to this outcome study suggest that a combined medical and invasive approach may be superior to medical therapy alone, at least regarding subclinical CAD progression. This is in agreement with 2 small randomized trials that

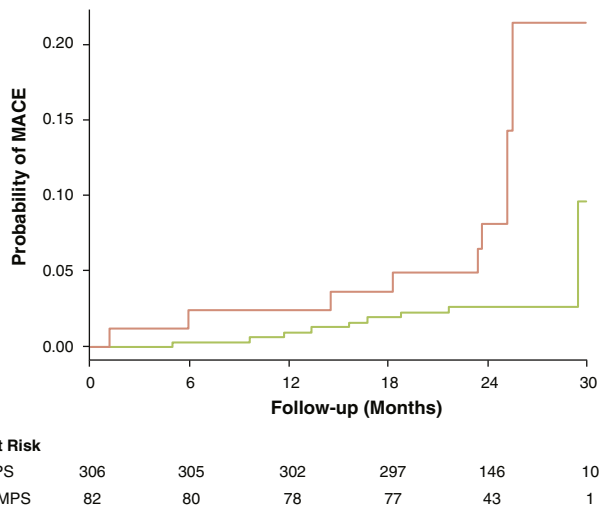

FIGURE 2 Comparison of the Probability of Symptomatic CAD Progression in Patients With Normal Versus Abnormal MPS

Kaplan-Meier estimates of the probability of a major adverse cardiac event (MACE) (primary endpoint) in patients with **(pink)** versus without **(green)** abnormal myocardial perfusion single- photon emission computed tomography (MPS) (p = 0.011; see Table 2). Abbreviation as in Figure 1.

TABLE 4 Two-Year Medical Therapy and Relevant Laboratory Findings in Patients With Normal Versus Abnormal MPS

	Patients With Normal MPS (n = 291)	Patients With Abnormal MPS (n = 73)	p Value*
Antiplatelet therapy	53	88	<0.0001
Oral anticoagulants	5	15	0.0044
Beta-blocker	31	92	<0.0001
Calcium antagonist	29	33	0.60
Nitrates	1	0	0.88
Statins	60	96	<0.0001
ACE-I/ARB	76	84	0.22
Diuretics	48	62	0.05
Oral glucose-lowering therapy	78	71	0.26
Insulin	50	55	0.50
HbA1c, %	7.4 ± 1.3	7.4 ± 1.2	0.98
Total cholesterol, mmol/l	4.5 ± 1.1	3.6 ± 0.9	<0.0001
LDL cholesterol, mmol/l	2.4 ± 0.9	1.7 ± 0.8	<0.0001
HDL, mmol/l	1.26 ± 0.4	1.20 ± 0.4	0.03
Systolic blood pressure, mm Hg	131.0 ± 17.0	132.0 ± 19.0	0.93

Values are % or mean ± SD. *p values were calculated with the use of a Mann-Whitney *U* test for quantitative variables and a chi-square test for qualitative variables.

ACE-I/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MPS = myocardial perfusion single-photon emission computed tomography.

TABLE 5 Two-Year Outcome Events in Patients With Abnormal MPS Randomized to the Invasive Versus Medical Strategy

	Medical Strategy (n = 39)	Invasive Strategy (n = 43)	HR/OR (95% CI)	p Value
Patients with MACE	6 (15.4)	2 (4.7)	0.36 (0.05–1.81)	0.215
Cardiac death	2 (4.7)	0 (0.0)	0.91 (0–N.A.)	0.999
Myocardial infarction	1 (2.6)	2 (4.7)	1.88 (0.17–20.74)	0.607
Revascularization	6 (15.4)	0 (0.0)	0.00 (0–inf)	0.998
Scintigraphic ischemia/new scar*	19 (54.3)	6 (15.8)	0.16 (0.05–0.45)	<0.001
Patients with "overt or silent CAD progression"*	20 (57.1)	6 (15.8)	0.14 (0.04–0.40)	<0.001

Values are n (%). *p values from Cox proportional-hazards survival model (HR and 95% CI) except for scintigraphic ischemia or new scar and "overt or silent CAD progression" (OR and 95% CI from generalized linear model).

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; inf = infinity; MACE = major acute cardiac events; MPS = myocardial perfusion single-photon emission computed tomography; N.A. = not applicable; OR = odds ratio.

found revascularization improved survival in patients with silent CAD and stable disease (17,18); the ACIP (Asymptomatic Cardiac Ischemia Pilot) and the SWISSI I (Swiss Interventional Study on Silent Ischaemia type I) study. However, they did not focus on patients with diabetes. A recent observational study challenged this notion in patients after revascularization (24), but this study was subject to a major selection bias (25). A retrospective study from the Mayo Clinic found an improved survival in a subset of asymptomatic patients with diabetes without known CAD and high-risk MPS undergoing bypass surgery (26), and scintigraphic follow-up studies of 2 large treatment trials comparing revascularization with medical therapy showed a greater ischemia reduction in revascularized compared with medically managed patients (27,28), also suggesting a benefit of revascularization similar to what was found in the present study. In fact, this high risk in BARDOT substantiated by myocardial ischemia may be the major reason for outcome differences between BARDOT and BARI-2D (29), in which coronary angiography results were known before randomization. This points to the importance of ischemia evaluation to guide further management decisions, as tested in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA NCT01471522) project.

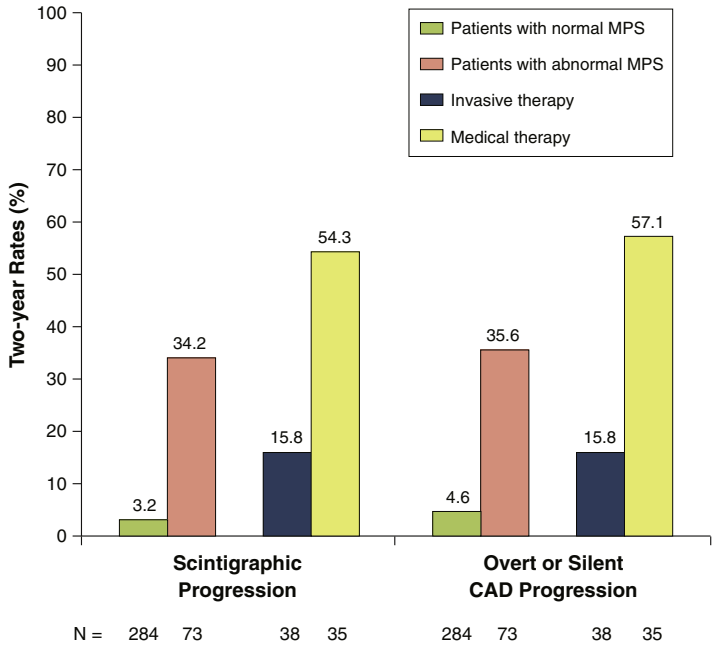

FIGURE 3 Comparison of 2-Year Rates of Scintigraphic Progression and "Overt or Silent CAD Progression" in Patients With Normal Versus Abnormal MPS and Patients With Abnormal MPS Managed Medically Versus Invasively

Note the higher rates of ischemia or new scar in patients with **(pink)** versus without abnormal MPS **(green) (both left graphs)** and the parallel findings of "overt or silent CAD progression" **(right graphs)**. Note also the higher rates of scintigraphic progression and of "overt or silent CAD progression" in patients with abnormal MPS managed medically **(yellow)** versus invasively **(blue)**; for p values see Tables 2 and 4. Abbreviations as in Figure 1.

CONCLUSIONS

If patients with diabetes are clinically at high risk of CAD as in BARDOT, they should be considered for ischemia testing. If there is no evidence of CAD as in about 80% of them, the 2-year outcome will be benign without further anti-ischemic therapy and no need for repeat testing within 4 to 5 years. However, in about 20% of patients with abnormal MPS, anti-ischemic therapy should be advised because every third patient will experience MACE or therapy-refractory silent CAD. Thus, these findings should directly impact daily practice and lead to corresponding adjustments in current guidelines. The optimal type of therapy is still open to debate. The present pilot study findings suggest that a combined

medical and invasive strategy may at least reduce scintigraphic but not symptomatic CAD progression compared with medical therapy alone. An appropriately sized randomized controlled trial is needed to settle this question.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Michael J. Zellweger, Cardiology Department, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail: michael.zellweger@usb.ch.

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KEY WORDS coronary artery disease, diabetes type 2, myocardial perfusion SPECT, risk stratification, silent ischemia, treatment

APPENDIX For supplemental tables and figures, please see the online version of this article.