Obstructive and nonobstructive coronary artery disease in long-lasting type 1 diabetes: a 7-year prospective cohort study

Ewa Konduracka[1], Grażyna Cieślik[2], Maciej T. Małecki[3], Grzegorz Gajos[1], Aleksander Siniarski[1], Krzysztof P. Malinowski[4], Magdalena Kostkiewicz[5], Lucyna Mastalerz[6], Jadwiga Nessler[1], Wiesława Piwowarska[1]

1 Department of Coronary Disease and Heart Failure, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland
2 Diabetology Consulting Unit, Centre for Treatment of Civilization-Induced Diseases, Kraków, Poland
3 Department of Metabolic Diseases, Jagiellonian University Medical College, Kraków, Poland
4 Institute of Public Health, Faculty of Health Science, Jagiellonian University Medical College, Kraków, Poland
5 Department of Nuclear Medicine, John Paul II Hospital, Kraków, Poland
6 Department of Internal Medicine, Jagiellonian University Medical College, Kraków, Poland

KEY WORDS

long-lasting type 1 diabetes, nonobstructive coronary disease, obstructive coronary disease

ABSTRACT

INTRODUCTION It is widely believed that patients with diabetes are at increased risk of severe and premature coronary artery disease (CAD) when compared with nondiabetic individuals.

OBJECTIVES The aim of the study was to evaluate the prevalence, 7-year incidence, predictors, and outcomes of obstructive and nonobstructive CAD in patients with long-lasting type 1 diabetes.

PATIENTS AND METHODS We enrolled 2330 patients at a median age of 50 years and a median diabetes duration of 32 years. All participants underwent diagnostic workup for CAD with an exercise treadmill test (ETT), single-photon emission computed tomography (SPECT), or both. Coronary angiography was performed in patients with abnormal ETT/SPECT results and repeated during the study if clinically indicated.

RESULTS The prevalence of obstructive and nonobstructive CAD was 6.9% and 42%, respectively, while the 7-year incidence, 1.9% and 7.4%, respectively. Of the 160 revascularized patients, 38% underwent complete revascularization. Acute coronary syndromes were reported in 3.6% of patients (54% with nonobstructive CAD). Cardiac deaths were reported in 1.07% of the population, and only in patients with obstructive CAD. Age, diabetes duration, hypertension, and renal failure were predictors of obstructive CAD, while type 1 diabetes duration, glycated hemoglobin A_{1c} levels, frequent severe hypoglycemia, hypertension, triglyceride levels, renal failure, and cardiac autonomic neuropathy predicted nonobstructive CAD.

CONCLUSIONS Nonobstructive CAD was the most frequent coronary complication in patients with type 1 diabetes. Both obstructive and nonobstructive CAD showed a similar incidence of nonfatal outcomes and selected predictors. Positive ETT/SPECT results were related to glycemic control only in patients with nonobstructive CAD.

Correspondence to:
Ewa Konduracka, MD, PhD, Department of Coronary Disease and Heart Failure, Institute of Cardiology, Faculty of Medicine, Jagiellonian University Medical College, John Paul II Hospital, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48 12 614 22 18, email: ekonduracka@interia.eu
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INTRODUCTION Type 1 diabetes is a predominant form of diabetes in children, adolescents, and young adults.[1] Compared with type 2 diabetes, the occurrence of type 1 diabetes has been growing less dynamically and fewer studies have investigated its complications.[1-6]

Although type 1 and type 2 diabetes are 2 distinct disease entities, the differences between them do not seem to have been adequately addressed in the literature. These differences result not only from the varied prevalence of the 2 conditions but also from their underlying pathophysiology and comorbidities. Type 1 diabetes is characterized by absolute insulin deficiency and usually occurs in persons without concomitant disorders at diagnosis.[1,7,8] On the other hand, type 2 diabetes typically coexists with insulin resistance and numerous cardiovascular risk factors.[8]

It is widely believed that patients with diabetes are at increased risk of severe and premature obstructive coronary artery disease (CAD), compared with nondiabetic individuals.[1,7,8] Nonetheless, the real prevalence of vascular complications, including obstructive and nonobstructive CAD, in patients with type 1 diabetes remains unknown.

The aim of the present study was to evaluate the prevalence, 7-year incidence, predictors, and outcomes of obstructive and nonobstructive CAD in patients with long-lasting type 1 diabetes.

PATIENTS AND METHODS

Patients Between the years 2001 and 2003, we enrolled 2350 patients with a clinical diagnosis of type 1 diabetes, defined as previously described,[9] and a duration of diabetes longer than 15 years. The study population was randomly selected (by the computer random number generator) from patients treated in diabetology clinics in 3 southern Polish voivodships (Małopolska, Podkarpackie, and Świętokrzyskie).

Patients underwent diagnostic procedures for CAD (see below), as well as the assessment of cardiovascular risk factors and chronic diabetic complications at baseline and at 7 years of follow-up. During follow-up, we contacted participants as well as their diabetologists and family doctors at the place of residence, by phone or email every 6 months (or when necessary). Patients could contact us at any time in case their health status deteriorated. If necessary, patients were invited to our department for a comprehensive differential diagnosis and treatment during follow-up. At baseline, 20 patients refused to give informed consent to participate in the study, resulting in a study sample of 2330 participants. A total of 2303 patients completed the study. The distribution of patients at baseline and during follow-up is presented in FIGURE 1.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Jagiellonian University Medical College (KBET/335/B/2001, to EK). Each study participant provided written informed consent before enrollment.

Diagnostic procedures All participants underwent physical examination, medical history taking, assessment of chronic diabetes complications, echocardiography, exercise treadmill test (ETT) or single-photon emission computed tomography (SPECT) with technetium 99m (^{99m}Tc), as well as laboratory tests.

SPECT was performed when ETT was contraindicated or not suitable to exclude myocardial ischemia, namely, in cases of silent myocardial ischemia on ETT, preexcitation syndrome on electrocardiography, pacemaker, atrial fibrillation or flutter, resting or asymptomatic exercise-related left bundle branch block (LBBB), exercise-related ventricular tachycardia in patients without typical angina, resting repolarization abnormalities, exercise intolerance (shortness of breath, fatigue, or nausea already at a workload of 5 metabolic equivalents), and an insufficient increase in arterial blood pressure of less than 30 mm Hg or a decrease below the resting blood pressure value. Some patients underwent ETT as the first procedure, followed by SPECT, according to the criteria described above. The procedures were repeated at 7 years of follow-up and, additionally, when necessary during the study.

The criteria for positive ETT results included chest pain, shortness of breath increasing on exercise and resolving at rest, and one of the following: 1) horizontal or downsloping ST-segment depression ≥1 mm in 2 or more electrocardiographic leads 60 to 80 ms from the J point in 3 consecutive beats in patients without preexcitation, atrial fibrillation or flutter, pacemaker, resting LBBB, resting repolarization abnormalities; or 2) exercise-related ventricular tachycardia or LBBB in patients with typical angina symptoms.

The criteria for positive SPECT results included reversible perfusion defects in 2 or more of the 17 segments, or reversible perfusion defects in over 10% of the myocardial area, or multiple ischemic perfusion defects in more than 1 coronary artery territory. Participants with inability or contraindications to exercise underwent SPECT with vasodilator or inotropic agents. During follow-up, ETT/SPECT was repeated when necessary.

Subsequently, quantitative coronary angiography was used for segmental analysis of the coronary arteries in patients with positive results of ETT/SPECT at baseline and was repeated during follow-up and at the end of the study if clinically indicated (acute coronary syndrome [ACS] during follow-up, abnormal ETT/SPECT results).

Based on coronary angiography findings and positive ETT/SPECT results, patients were divided into 2 major subgroups: 1) patients with obstructive CAD, defined as coronary stenosis of 70% or greater in the epicardial coronary artery, or of 50% or greater in the left main coronary artery, or when the fractional flow reserve was equal to or less than 0.80 in patients with borderline coronary lesions on angiography; and 2) patients with nonobstructive CAD: type A, defined as normal coronary anatomy (<20% stenosis) in all coronary arteries, and type B, defined as any stenosis of 20% or greater but less than 70%, narrowing in any epicardial artery, or stenosis of 20% or greater but less than 50% in the left main coronary artery.

Premature obstructive CAD was defined as a diagnosis of obstructive CAD in patients under 45 years of age. Complete revascularization was defined as treatment with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) of any lesion with stenosis of 70% or greater in the vessels with a diameter of 2 mm or higher, or stenosis of 50% or greater in the left main coronary artery supplying the viable

TABLE 1 Patient characteristics and treatment at baseline and at 7-year follow-up

Variables	Baseline (n = 2330)	At 7 years (n = 2303)	*P* value
Age, y	50 (40–59)	57 (47–66)	–
Female sex, n (%)	1126 (48.3)	1126 (48.9)	–
Diabetes duration, y	32 (22–44)	39 (29–51)	–
BMI, kg/m²	23.4 (21.0–24.6)	23.7 (22.0–26.5)	<0.0001
SBP, mm Hg	135.0 (127.0–140.0)	130.0 (120.0–135.0)	<0.0001
DBP, mm Hg	87.0 (80.0–89.0)	78.0 (70.0–83.0)	<0.0001
Medical history			
Cigarette smoking, n (%)	84 (3.6)	60 (2.6)	<0.0001
Heart failure, n (%)	175 (7.5)	183 (8.0)	0.01
Hypertension, n (%)	1749 (75.1)	1767 (76.7)	0.001
Impaired renal function[a], n (%)	559 (21)	628 (27.2)	<0.0001
End-stage renal disease, n (%)	21 (0.9)	27 (1.1)	0.007
Albuminuria, n (%)	422 (18.1)	518 (22.5)	<0.0001
Peripheral neuropathy, n (%)	1118 (48)	1290 (56)	<0.00001
Peripheral atherosclerosis, n (%)	198 (8.5)	212 (9.2)	<0.0001
Cardiac autonomic neuropathy, n (%)	508 (21.8)	532 (23.1)	<0.0001
Frequent severe hypoglycemia, n (%)	256 (11.0)	268 (11.6)	<0.0001
Any retinopathy, n (%)	1701 (73)	1819 (78.9)	0.004
Proliferative retinopathy, n (%)	839 (36)	869 (37.7)	0.03
Laboratory investigations			
HbA_{1c}, %	7.6 (7.0–8.1)	7.3 (6.8–8.2)	<0.0001
eGFR, ml/min/1.73 m²	90.0 (80.0–99.0)	85.0 (76.0–93.0)	<0.0001
LDL-C, mmol/l	3.0 (2.4–3.4)	2.3 (1.7–2.7)	<0.0001
HDL-C, mmol/l	1.1 (0.8–1.4)	1.2 (1.0–1.5)	<0.0001
Triglycerides, mmol/l	1.3 (1.0–1.5)	0.9 (0.7–1.2)	<0.0001
Pharmacological treatment			
Statins, n (%)	1084 (46.5)	1105 (48.0)	<0.0001
ACEIs, n (%)	1407 (60.4)	1427 (62.0)	<0.0001
ARBs, n (%)	334 (14.3)	350 (15.2)	<0.0001
β-Blockers, n (%)	470 (20.2)	492 (21.4)	<0.0001
CCBs, n (%)	1509 (64.8)	1639 (71.2)	<0.0001
Diuretics, n (%)	321 (13.8)	405 (17.6)	<0.0001
Fibrates, n (%)	31 (1.3)	51 (2.2)	<0.0001
Antiplatelet agents, n (%)	1958 (84.0)	942 (84.3)	0.0009

Data are shown as median (interquartile range) unless otherwise indicated.

a Defined as eGFR <60 ml/min/1.73 m²

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, channel calcium blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

myocardium. Coronary lesions not suitable for revascularization were defined as chronic total occlusions in single-vessel disease not involving the left anterior descending artery, side small branch stenoses or distal coronary lesions, and diffuse atherosclerotic lesions from the proximal to distal beds, leading to a thread-like appearance with small (<2 mm) distal runoff. Hypertension was defined as a blood pressure of 140/90 mm Hg or higher on at least 2 separate measurements, or the use of antihypertensive drugs.

Cardiac autonomic neuropathy (CAN) was defined as the impairment of autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics after exclusion of other causes of dysautonomia.[10,11] In our study, CAN was diagnosed by cardiovascular autonomic reflex tests based on the assessment of heart rate response to deep breathing, standing, the Valsalva maneuver (not advisable in patients with advanced proliferative retinopathy); blood pressure response to standing; and heart rate variability time and frequency domain indices. CAN was diagnosed when abnormalities were present in more than 1 test.[10,11]

A smoker was defined as a patient smoking at least 1 cigarette, pipe, or cigar daily, or as a patient who had stopped smoking in the past 3 months.

Severe hypoglycemia was defined as an event requiring assistance of another person to administer carbohydrates, glucagon, or both. In fact, plasma glucose concentrations are not always available during the event, but the recovery following normalization of plasma glucose is considered sufficient evidence that the event had been induced by low plasma glucose concentrations.[12] Frequent severe hypoglycemia was defined as more than 3 episodes per year. Diabetic retinopathy was diagnosed based on ophthalmologic examination with fluorescein angiography at baseline and at the end of follow-up.

Laboratory assessment Glycated hemoglobin A_{1c} (HbA_{1c}) levels were assessed using high-performance liquid chromatography. The final results of HbA_{1c} (at the end of follow-up) were calculated as the median HbA_{1c} concentrations during the 7-year follow-up.

Albuminuria was diagnosed with a urinary albumin-to-creatinine ratio in a random spot urine collection. Increased urinary albumin excretion was defined as a creatinine clearance of 30 mg/g or higher in at least 2 of 3 consecutive tests, collected within a 3- to 6-month period.

All laboratory measurements were performed in the same central laboratory. The results are presented in TABLE 1.

Study outcomes The primary study outcome was the diagnosis of obstructive or nonobstructive CAD. The secondary endpoint was the incidence of ACS (such as myocardial infarction or unstable angina) and of cardiac death during the 7-year follow-up. The outcomes were evaluated independently by an adjudication committee consisting of experienced cardiologists.

Pharmacological treatment During the study, patients were treated using the regimen of multiple (4 or more) insulin injections or an insulin pump (10 patients). All participants were treated in agreement with the current cardiac and diabetes guidelines.

Statistical analysis Continuous variables were expressed as medians with the first and third quartiles, and categorical variables, as numbers and percentages. The analysis of variance or the Kruskal–Wallis test was applied where appropriate to compare continuous variables across the HbA_{1c} quartiles. For categorical variables, the χ^2 test was used. Baseline and follow-up data were compared using the paired *t* test or the Mann–Whitney test where appropriate for continuous variables and the Bowker test for categorical variables. All statistical tests were 2-sided with an α value of 0.05. A multiple regression analysis was used to assess the predictors of the prevalence of both obstructive and nonobstructive CAD. A logistic regression analysis was used to investigate the odds for the occurrence of new cases of obstructive and nonobstructive CAD during follow-up. The prevalence was defined as the total number of obstructive or nonobstructive CAD cases at baseline and at 7 years, calculated per 1000 participants, while the incidence was defined as the number of new obstructive or nonobstructive CAD cases in the study population per year over the 7-year follow-up, calculated per 1000 participants. The statistical analysis was performed using the JMP 13.1.0 software (SAS Institute Inc., Poland).

RESULTS The final study sample included 2330 patients with type 1 diabetes. The characteristics of the study population, as well as data on treatment and concomitant disorders, are shown in TABLE 1. At baseline, the ETT and SPECT were performed in 31% and 69% of the study group, respectively. Of the study group, 1130 patients (48.4%) showed positive ETT/SPECT results and underwent coronary angiography at baseline (FIGURE 1). Angiography was repeated during follow-up and at the end of the study if clinically indicated (ACS during follow-up, abnormal ETT/SPECT results).

Study outcomes, predictors, and follow-up The baseline prevalence and 7-year incidence were 6.9% and 1.9%, respectively, for obstructive CAD, and 41.6% and 7.4%, respectively, for nonobstructive CAD (TABLE 2 and FIGURE 1). Among patients with nonobstructive CAD, type A was observed in 72.5% and type B in 27.5% (FIGURE 1).

The multivariate analysis did not show significant differences between sexes in the occurrence of the predictors. The results of univariate and multivariate analyses in the whole study population are presented in TABLES 3 and 4. Diabetes duration, hypertension, and renal impairment were predictors of both obstructive and nonobstructive CAD, whereas HbA_{1c} levels, CAN, frequent severe hypoglycemia, and triglyceride levels were predictors only of nonobstructive CAD. On the other hand, aging was a predictor only of obstructive CAD (TABLE 3).

At diagnosis, patients with obstructive CAD were older than those with nonobstructive CAD: median age, 61 years (range, 56–67 years) vs 51 years (range, 46–62 years) ($P = 0.001$). Obstructive CAD was more prevalent in men than in women: 108 (67.5%) vs 52 (32.5%), $P < 0.0001$, and women were older than men at diagnosis of obstructive CAD: median age, 64 years (range, 59–70 years) vs 55 years (range, 52–67 years), $P = 0.003$. Premature obstructive CAD was revealed in only 0.09% of the patients. About 60% of patients with nonobstructive CAD had albuminuria, while 54% had proliferative retinopathy.

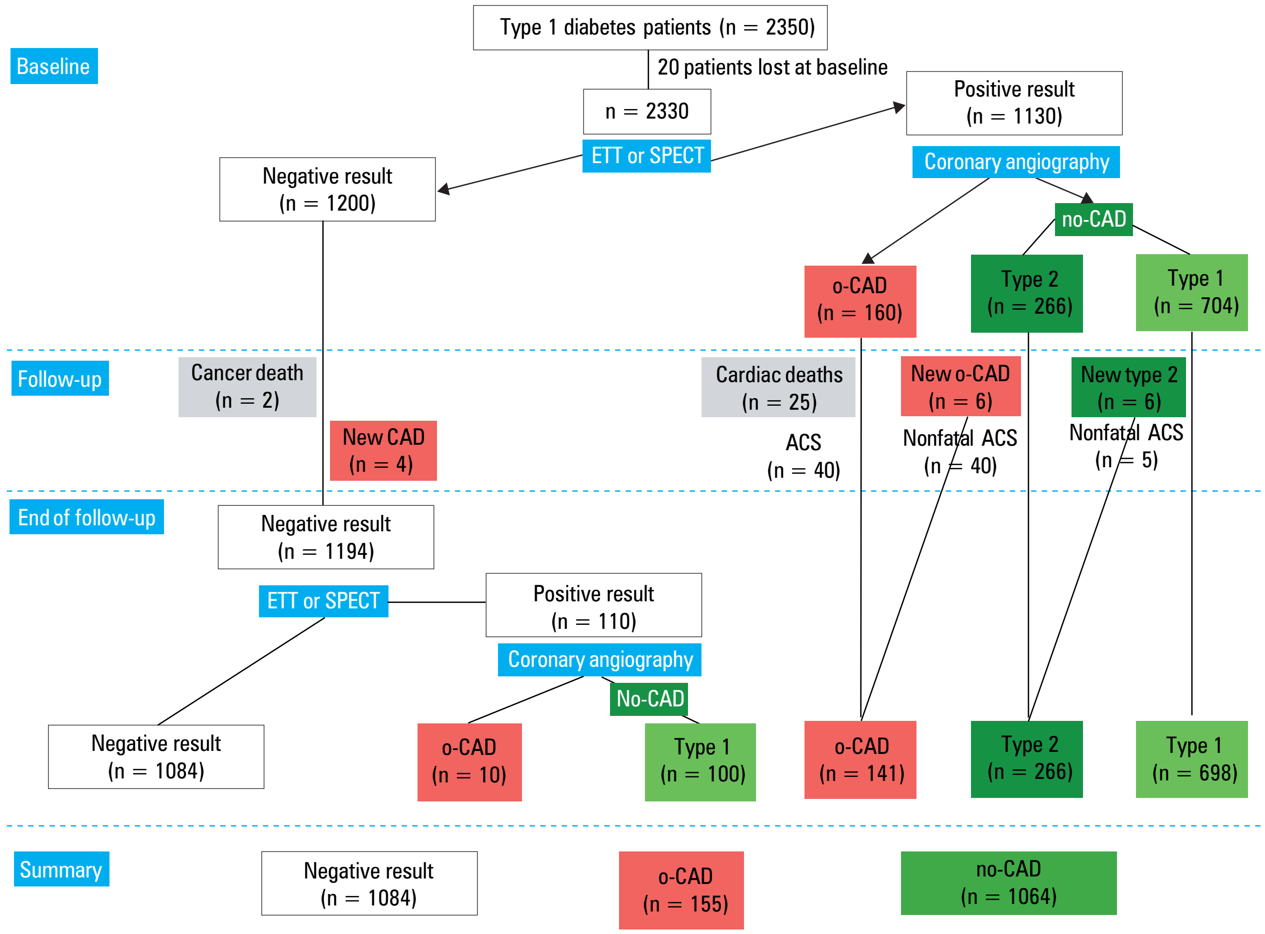

FIGURE 1 Patient flow through the study

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; ETT, exercise treadmill test; no-CAD, nonobstructive CAD; o-CAD, obstructive CAD; SPECT, single-photon emission computed tomography; T1D, type 1 diabetes; Type 1, normal coronary anatomy (<20% stenosis) in all coronary arteries; Type 2, any stenosis of 20% or higher but less than 70%, narrowing in any epicardial artery, or stenosis of 20% or higher but less than 50% in the left main artery

TABLE 2 Prevalence and incidence of significant obstructive and nonobstructive coronary artery disease in patients with type 1 diabetes

Variable	Measure	HbA_{1c} quartiles, % (mmol/mol)				
		<7.0 (<53) (n = 528)	7.00–7.60 (53–60) (n = 631)	7.61–8.00 (61–64) (n = 589)	>8.00 (>64) (n = 582)	Total (n = 2330)
Nonobstructive CAD prevalence (baseline)	n (%)	48 (9.1)	138 (21.9)	350 (59.4)	434 (74.6)	970 (41.6)
Nonobstructive CAD incidence	New cases (%)	5 (1.04)	24 (4.9)	33 (13.8)	38 (25.7)	100 (7.4)
Obstructive CAD prevalence (baseline)	n (%)	34 (6.4)	62 (10.0)	42 (7.1)	22 (3.8)	160 (6.9)
Obstructive CAD incidence	New cases (%)	15 (3.0)	16 (2.8)	5 (0.9)	4 (0.7)	40 (1.9)

Abbreviations: see **TABLE 1** and **FIGURE 1**

Of the 160 patients with obstructive CAD, 16% had 1-vessel disease, 44% had 2-vessel disease, and 40% had 3-vessel or multivessel disease.

Clinical symptoms of ischemia Typical angina on exertion was noted in 45% of patients with obstructive CAD and in 43% of those with nonobstructive CAD, while exercise intolerance was observed in 50% of patients with obstructive CAD and 49% of those with nonobstructive CAD; 5% of patients with obstructive CAD and 8% of those with nonobstructive CAD reported no complaints.

Revascularization procedures At baseline, among 160 patients with obstructive CAD referred for revascularization, only 38% underwent complete revascularization, whereas 42% underwent incomplete revascularization and 20% did not undergo any procedure (30 patients had lesions unsuitable

TABLE 3 Predictors of obstructive coronary artery disease in type 1 diabetes

Predictors of obstructive CAD	OR	95% CI	*P* value
Univariate analysis			
Frequent severe hypoglycemia	1.4	1.2–3.0	0.002
Diabetes duration per year	2.0	1.5–3.5	0.001
eGFR <60 ml/min/1.73 m²	0.8	0.1–2.2	0.003
Hypertension	2.9	2.1–5.0	0.001
HDL-C, mmol/l	0.1	0.5–1.9	0.01
Albuminuria	1.5	1.2–2.9	0.001
Age per year	3.4	1.5–4.1	<0.0001
Multivariate analysis			
Age per year	1.9	1.4–2.3	<0.0001
Diabetes duration per year	1.3	1.07–3.2	0.009
Hypertension	2.1	1.4–2.9	<0.0001
eGFR <60 ml/min/1.73 m²	1.6	1.0–3.4	0.02

Abbreviations: OR, odds ratio; others, see TABLE 1 and FIGURE 1

TABLE 4 Predictors of nonobstructive coronary artery disease in type 1 diabetes

Predictors of nonobstructive CAD	OR	95% CI	*P* value
Univariate analysis			
Age per year	1.1	1.1–2.2	0.01
Diabetes duration per year	1.9	1.0–2.6	<0.0001
HbA_{1c}, %	2.7	2.4–3.1	<0.0001
eGFR <60 ml/min/1.73 m²	1.0	0.9–2.3	0.003
Hypertension	2.8	1.2–5.4	<0.0001
Triglycerides, mmol/l	1.6	1.3–2.0	<0.0001
CAN	1.9	1.2–3.0	<0.0001
LDL-C, mmol/l	1.2	1.0–2.1	0.03
Frequent severe hypoglycemia	1.5	1.0–2.9	0.002
Multivariate analysis			
Diabetes duration per year	1.4	1.0–2.3	0.001
HbA_{1c}, %	2.0	1.8–2.9	<0.0001
Frequent severe hypoglycemia	1.3	1.0–2.0	0.001
Hypertension	1.9	1.3–2.3	<0.00001
Triglycerides, mmol/l	1.2	1.0–2.0	0.02
eGFR <60 ml/min/1.73 m²	1.5	1.1–2.9	0.0003
CAN	1.1	1.0–2.1	0.01

Abbreviations: CAN, cardiac autonomic neuropathy; others, see TABLE 1, TABLE 3, and FIGURE 1

for any revascularization and 2 patients did not give their consent to undergo CABG). PCI with drug-eluting stent implantation was performed in 80% of patients undergoing revascularization if technically feasible and safe for the patients. Surgical revascularization was performed only in 20% of patients, as the remaining ones had lesions not suitable for CABG.

In patients with multivessel CAD, left main CAD, or when appropriate, the choice of the revascularization method was at the discretion of cardiologists and a cardiac surgeon.

Cardiac events During follow-up, ACSs were diagnosed in 85 patients (3.6% of the study population). Among patients with ACS, 47% had previously diagnosed obstructive CAD (5 patients, restenosis after revascularization; 35 patients, incomplete revascularization performed at baseline).

Surprisingly, the incidence of ACS in patients with nonobstructive CAD was similar to that in patients with obstructive CAD. Participants with nonobstructive CAD type 2 represented 47% of all ACS cases, whereas those with type 1, only 6%. At diagnosis of ACS, 39 patients underwent successful PCI, and the remaining ones received pharmacological treatment. All patients with ACS were symptomatic with chest pain, except 2 participants who had unexplained dyspnea before ACS diagnosis.

Of the whole study population, 1.15% were lost to follow-up. Two patients died due to cancer. Of the 25 patients with previously diagnosed obstructive CAD, 4 patients treated with PCI at baseline died during follow-up due to severe hypoglycemia and sudden cardiac arrest, 10 patients who underwent incomplete or no revascularization died due to ACS with subsequent cardiogenic shock, 9 patients with incomplete revascularization died due to refractory heart failure, and 2 patients after successful revascularization at baseline died a few years later due to pulmonary embolism and cardiogenic shock.

DISCUSSION In this study, we attempted to assess the current prevalence and incidence, as well as the predictors and outcomes, of obstructive and nonobstructive CAD in a real-life cohort of 2330 patients with long-lasting type 1 diabetes. Although this study was not designed to investigate specific interventions, we observed an improvement in glycemic control as well as treatment of hypertension and dyslipidemia during the 7-year follow-up. The improvement of glycemic control was associated with an increase in body mass index and the number of hypoglycemia episodes in some patients, but we also noted an improvement of the lipid profile. Of note, despite low rates of statin use (less than half of the population in our study), the incidence of obstructive CAD was relatively low. However, the evidence for clinical benefits of statin use in patients with type 1 diabetes is limited. A meta-analysis by the Cholesterol Treatment Trialists Collaborators revealed a nonsignificant 21% relative risk reduction of major cardiovascular events among 1466 patients with type 1 diabetes.[13]

There is also much confusion about symptoms of myocardial ischemia in diabetic population, and it is widely believed that patients with CAD are commonly symptomless. This is in contrast to our results because most patients with both obstructive and nonobstructive CAD were symptomatic, but the most common symptom was exercise intolerance, while typical angina was reported in over 40% of patients with ischemia. Therefore, it is extremely important to distinguish exercise intolerance as a separate symptom of ischemia in diabetic patients after exclusion of other causes.

Despite long diabetes duration, the prevalence of obstructive CAD was consistent with angiography or autopsy findings from previous studies in the general nondiabetic population at a similar age.[14,15] Moreover, in our study, we did not confirm a higher prevalence of premature obstructive CAD in comparison with data reported for the general population in earlier studies.[1] We also revealed a low incidence of obstructive CAD. In contrast, the cumulative incidence of obstructive CAD in previously published studies ranged from 2.1% to 19%, with most of them reporting a cumulative incidence of approximately 15 years of follow-up.[8,16,17]

Some studies indicated that diabetes appears to attenuate the protective effect of the female sex on the development of cardiovascular complications.[18] This is in contrast to our results because in our population, obstructive CAD was less common in women, and women were also older than men at diagnosis of obstructive CAD.

Although in the present study the prevalence of obstructive CAD was low, we found that ETT and ^{99m}Tc-sestamibi SPECT, which are recommended as the first-line noninvasive diagnostic procedures in cardiological guidelines, have a limited diagnostic value related to their sensitivity and specificity in detecting myocardial ischemia. Therefore, it is possible that the percentage of obstructive CAD cases was slightly underestimated. This constitutes the first limitation of our study. On the other hand, during the 7-year follow-up, most patients with undiagnosed obstructive CAD would have ACS or other signs of ischemia. However, we were in contact with the patients and their doctors during follow-up, and we also assessed participants at the end of follow-up, so any events were unlikely to have been missed.

In our study, patients with nonobstructive CAD and ischemia represented a larger and more heterogeneous group than those with obstructive CAD. The nonobstructive group encompassed patients with normal epicardial arteries and those with nonsignificant lesions on angiography. In patients with nonobstructive CAD, the presence of persistent chest pain or significant exercise intolerance, along with coexisting ischemia on ETT/SPECT, allowed us to establish the diagnosis of microvascular disease. On the other hand, due to inherent limitations of ETT/SPECT and all current methods for the diagnosis of microvascular disease, the number of cases was certainly underestimated. Furthermore, we realize that microvascular disease may occur in some patients together with obstructive CAD, so the prevalence of microvascular disease may also have been underestimated. This constitutes another limitation of our study. On the other hand, the incidence of nonfatal ACS in patients with nonobstructive CAD type 2 was similar to that in patients with obstructive CAD, whereas in patients with nonobstructive CAD type 1, the incidence was definitely lower than in participants with obstructive CAD.

The incidence of ACS and cardiac deaths in the whole study population was relatively low. This is in line with the results of Rawshani et al,[19] who reported an incidence of ACS of 2.4% and a reduction of fatal outcomes among patients with type 1 diabetes, with no differences in comparison with nondiabetic controls.[20] However, other studies reported a cumulative mortality for CAD of 6% to 8%.[1,8,21]

In patients with obstructive CAD who undergo incomplete or no revascularization, the prognosis is still poor.[21] In our study, 15.6% of patients with obstructive CAD died during follow--up because of coronary lesions unsuitable for revascularization.

In the present study, diabetes duration, hypertension, and kidney failure were independent predictors of both obstructive and nonobstructive CAD, while frequent severe hypoglycemia, HbA_{1c} levels, and elevated serum triglyceride levels predicted the prevalence of nonobstructive CAD. The effect of diabetes duration, hypertension, kidney failure, and lipid disorders on the incidence of vascular complications in this population is well established in clinical studies.[1,22,23]

The effects of hyperglycemia, hypoglycemia, and glycemic variability on the development of cardiovascular complications have been widely discussed; however, their influence on the rate of nonobstructive CAD has not been evaluated in clinical studies.[24-26] In our study, hyperglycemia increased the risk of nonobstructive CAD but had no effect on the prevalence of obstructive CAD. The results of Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications also confirmed the relationship between chronic hyperglycemia and microvascular, but not macrovascular, complications.[27] Similarly to our findings, hyperglycemia was not a predictor of CAD in a 10-year follow-up report from the Pittsburgh Epidemiology of Diabetes Complications and Eurodiab studies,[1,17] while the importance of tight glycemic control for protection against CAD has been reported in other papers.[1,28]

Our study revealed that nonobstructive CAD with ischemia symptoms as a microvascular disease is the most common coronary complication in patients with type 1 diabetes. On the other hand, macrovascular complications are more common in type 2 than in type 1 diabetes.[5,6,29-33] Furthermore, macrovascular complications in patients with type 2 diabetes are often recognized earlier than diabetes itself.[33,34]

Obstructive and nonobstructive CAD differs in prevalence but has similar nonfatal outcomes and shares the same predictors including diabetes duration, hypertension, and renal failure. Positive results of ETT/SPECT with concomitant clinical symptoms of ischemia are related to glycemic control, CAN, frequent severe hypoglycemia, triglyceride levels in patients with diabetes and nonobstructive CAD, but not in those with obstructive CAD. In the era of modern therapy of diabetes and concomitant disorders, the prevalence, incidence, predictors, and outcomes of obstructive and nonobstructive CAD should be continuously evaluated to identify patients requiring personalized and intensified treatment.

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