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

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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 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 A1c 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.

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.1,6 On the other hand, type 2 diabetes typically coexists with insulin resistance and numerous cardiovascular risk factors.1
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. 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, 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 (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
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. 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 variabili-
ty 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 admin-
ter carbohydrates, glucagon, or both. In fact, plas-
ma glucose concentrations are not always avail-
dable during the event, but the recovery follow-
ing normalization of plasma glucose is consid-
ered 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 retinop-
athy was diagnosed based on ophthalmologic ex-
amination with fluorescein angiography at base-
line and at the end of follow-up.

Laboratory assessment Glycated hemoglo-
bin A\textsubscript{c} (HbA\textsubscript{c}) levels were assessed using high-
performed liquid chromatography. The final
results of HbA\textsubscript{c}, (at the end of follow-up) were
calculated as the median HbA\textsubscript{c} 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 ex-
creption 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 pre-
sented 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 unsta-
able angina) and of cardiac death during the 7-year
follow-up. The outcomes were evaluated indepen-
dently by an adjudication committee consisting
of experienced cardiologists.

Pharmacological treatment During the study, pa-
tients were treated using the regimen of multi-
ple (4 or more) insulin injections or an insulin
pump (10 patients). All participants were treat-
ed in agreement with the current cardiac and di-
abetes guidelines.

Statistical analysis Continuous variables were ex-
pressed as medians with the first and third quar-
tiles, and categorical variables, as numbers and
percentages. The analysis of variance or the Krus-
kal–Wallis test was applied where appropriate to
compare continuous variables across the HbA\textsubscript{c}
 quartiles. For categorical variables, the \(\chi^2\) 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 sta-
tistical tests were 2-sided with an \(\alpha\) 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 ana-
lysis was used to investigate the odds for the occur-
cence of new cases of obstructive and nonobstruc-
tive CAD during follow-up. The prevalence was de-
efined as the total number of obstructive or nonob-
structive CAD cases at baseline and at 7 years, cal-
culated 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 per-
formed using the JMP 13.1.0 software (SAS Insti-
tute Inc., Poland).

RESULTS The final study sample included
2330 patients with type 1 diabetes. The charac-
teristics 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 base-
line (FIGURE 1). Angiography was repeated dur-
ing follow-up and at the end of the study if clini-
cally indicated (ACS during follow-up, abnormal
ETT/SPECT results).

Study outcomes, predictors, and follow-up The base-
line prevalence and 7-year incidence were 6.9%
and 1.9%, respectively, for obstructive CAD, and
41.6% and 7.4%, respectively, for nonobstruc-
tive 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 signifi-
cant differences between sexes in the occurrence
of the predictors. The results of univariate and
multivariate analyses in the whole study popu-
lation are presented in TABLES 3 and 4. Diabetes
duration, hypertension, and renal impairment
were predictors of both obstructive and nonob-
structive CAD, whereas HbA\textsubscript{c} levels, CAN, fre-
quent severe hypoglycemia, and triglyceride lev-
els 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) \((P = 0.001)\). Ob-
structive 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 pa-
tients with nonobstructive CAD had albumin-
uria, while 54% had proliferative retinopathy.
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 for revascularization).

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.

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.
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 |
| HbA₁c, %                         | 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   |
| HbA₁c, %                         | 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     | <0.0001 |
| 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. 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. 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.

Some studies indicated that diabetes appears to attenuate the protective effect of the female sex on the development of cardiovascular complications. 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}\text{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., 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. However, other studies reported a cumulative mortality for CAD of 6% to 8%. In patients with obstructive CAD who undergo incomplete or no revascularization, the prognosis is still poor. 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.

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. 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. 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, while the importance of tight glycemic control for protection against CAD has been reported in other papers.

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. Furthermore, macrovascular complications in patients with type 2 diabetes are often recognized earlier than diabetes itself.

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 non-obstructive CAD, but not in those with obstructive CAD. In the era of modern therapy of diabeties 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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CONTRIBUTION STATEMENT EK contributed to acquisition, analysis, and interpretation of data, as well as writing and revision of the manuscript. GC, MTTM, GG, and AS contributed to acquisition and analysis of data. KPM contributed to analysis of data and statistical data analysis. MK, LM, WP, and JN contributed to acquisition of data, analysis and interpretation of data, as well as revision of the manuscript. EK made substantial contributions to conception and design of the study, analysis and interpretation of data, revision of the manuscript, and final approval of the version to be published. All authors read and approved the final manuscript.

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