Original Article

Clinical Predictors of Atheroma Progression Despite Optimal Glycemic Control in Early-Stage Diabetic Patients with Coronary Artery Disease: Insight from the DIANA Study

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Aim: In the DIANA (DIAbetes and diffuse coronary NArrowing) study, which evaluated the impact of glucose-lowering therapy in early-stage diabetics with coronary artery disease (CAD), optimal glycemic control resulted in reduced disease progression on angiography. However, despite having a favorable glycemic status, some patients continued to exhibit disease progression. Factors associated with disease progression despite optimal glucose control remain to be elucidated. We sought to investigate clinical characteristics associated with substantial atheroma progression in early-stage diabetic patients with CAD who achieve favorable glycemic control.

Methods: The DIANA study is a prospective randomized trial comparing the effects of lifestyle intervention and treatment with voglibose or nateglinide on disease progression on angiography in 302 CAD patients with impaired glucose tolerance/newly diagnosed diabetes. Of these patients, 137 CAD subjects who achieved optimal glycemic control were stratified according to the presence of disease progression on angiography: progressors ($n=64$) and non-progressors ($n=73$). Serial coronary angiography studies and quantitative coronary angiography analyses were conducted to evaluate disease progression. A multivariate analysis was performed to elucidate factors associated with disease progression.

Results: Despite the achievement of optimal glycemic control, atheroma progression was observed in 46% of the study subjects. The progressors exhibited lower decreases in systolic blood pressure (SBP: $p=0.007$) and reduced baseline total lesion lengths (TLL: $p=0.01$). The multivariate analysis demonstrated that a greater increase in SBP ($p=0.006$), treatment without statins ($p=0.03$) and the baseline TLL ($p=0.007$) were independently associated with disease progression.

Conclusions: Residual risk factors contribute to the progression of coronary atherosclerosis in early-stage diabetics who exhibit improvements in their glycemic status. The present findings underscore the need to intensively modify multiple risk factors during the early diabetic phase in order to prevent atheroma progression.

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Key words: Early-stage diabetes, Glycemic control, Residual risk factors, Disease progression

Introduction

In association with the global spread of abdominal adiposity, the prevalence of type 2 diabetes melli-

tus (DM) has increased worldwide¹. Diabetic patients are characterized by the presence of an accelerated progressive atheroma burden with a markedly increased incidence of adverse cardiovascular events²⁻⁵. Various

epidemiological studies have reported that vascular risks are increased in pre- or newly diagnosed diabetic patients⁶⁻⁹. Other imaging studies have also identified the presence of inflamed and extensive disease substrates in patients with impaired glucose tolerance (IGT)¹⁰⁻¹². These observations indicate that early-stage diabetic patients constitute an important therapeutic target for the prevention of future cardiovascular events.

Recently, the DIANA (Diabetes and Diffuse Coronary Narrowing) study, a prospective randomized trial evaluating the effects of glucose-lowering therapy in early-stage diabetics with coronary artery disease (CAD), demonstrated that favorable glycemic control is associated with reduced disease progression on angiography¹³. These results support the benefits of implementing glucose control strategies to prevent disease progression in the early stage of diabetes. However, not all patients with favorable glycemic control exhibit reduced progression of coronary atherosclerosis. Moreover, residual risk factors associated with atheroma progression despite the achievement of favorable glycemic control have not yet been characterized. Therefore, in the current study, we sought to investigate clinical characteristics correlated with substantial atheroma progression in early-stage diabetic patients who achieve favorable glycemic control. This subanalysis provided insight regarding important therapeutic targets contributing to the natural history of coronary atherosclerosis progression in early-stage diabetic patients with CAD.

Methods

Design Overview

The details of the DIANA study have been previously described¹³. Briefly, this study was a prospective randomized open-label blinded assessment of an end point trial conducted at 12 institutes in Japan (Trial Registration: UMIN-CTRID#0000107). A total of 302 angiographic CAD patients with both IGT or newly diagnosed DM and a glycosylated hemoglobin (HbA1c) level of <6.5% (6.9% NGSP 48mmol/mol) were enrolled. The patients were randomly assigned to receive lifestyle intervention ($n=101$), 0.9 mg of voglibose ($n=100$) or 180 mg of nateglinide ($n=101$)

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for one year. 75-g oral glucose tolerance tests were performed at baseline and at one year to assess serial changes in the glycemic status. Coronary atherosclerotic changes were evaluated on coronary angiography using a quantitative coronary arteriography (QCA) analysis at baseline and one year, as previously published in detail^{11, 13, 14}. In brief, diseased lesions were defined as major coronary segments narrowed to a diameter of ≤ 1.5 mm. The target lesion length (TLL) was determined by summing the lengths of all diseased lesions in three major coronary arteries. The percent change in TLL was calculated using the following formula for the assessment of angiographic disease progression:

Percent change in TLL (%) = $[(\text{TLL at one year} - \text{TLL at baseline}) / (\text{TLL at baseline})] \times 100$

The percent change in TLL was normally distributed, as shown in the p -value of the Shapiro-Wilk test ($p=0.34 > \alpha$ level of 0.05). The QCA data were assessed by two experienced cardiologists blinded to the subjects' glucose tolerance status and assigned group. The inter- and intraobserver correlation coefficients and percent error of the TLL measurements were 0.93 and $7.4 \pm 5.9\%$ and 0.98 and $3.9 \pm 2.6\%$, respectively. The DIANA study was approved by each participating center's institutional review board.

Study Subjects

This post hoc analysis included patients who exhibited an improvement in their glycemic status at one year regardless of the assigned therapy in the DIANA study. A total of 137 patients who exhibited an improvement in their glycemic status were stratified into two groups according to the presence of disease progression: progressors ($n=64$) and non-progressors ($n=73$).

Definitions of an Improvement in the Glycemic Status and Disease Progression

An improvement in the glycemic status was defined as reversion of the glycemic status on a 75-g oral glucose tolerance test from IGT to normal glucose tolerance or from DM to IGT/normal glucose tolerance. The World Health Organization criteria were used to classify the 75-g oral glucose tolerance test results¹⁵. We defined disease progression as an absolute change in TLL greater than 0 mm.

Statistical Analysis

The data for the clinical characteristics and use of baseline medications are expressed as the mean $\pm$ SD for continuous variables and the percentage for

Table 1. Baseline Clinical Characteristics and Use of Medical Therapies in the Progressors and Non-progressors

	Non-progressor (<i>n</i> = 73)	Progressor (<i>n</i> = 64)	<i>p</i> -value
Age (years)	64.4 ± 9.3	62.8 ± 9.8	0.36
Female (%)	19.0	8.9	0.11
IGT (%)	52.2	44.6	0.40
DM (%)	47.8	55.4	0.54
Hypertension (%)	85.6	86.1	0.86
Hypercholesterolemia (%)	65.0	68.1	0.71
Current smoker (%)	27.1	28.5	0.82
History of MI (%)	7.9	19.6	0.06
PAD (%)	3.1	3.5	0.90
Assigned therapy in the DIANA study			
Life-style intervention (%)	26.9	41.0	0.10
Voglibose (%)	33.3	35.7	0.78
Nateglinide (%)	39.6	23.2	0.06
Medication			
Statins			
baseline (%)	65.0	62.5	0.77
follow up (%)	85.7	76.1	0.19
Aspirin			
baseline (%)	100.0	100.0	1.00
follow up (%)	100.0	100.0	1.00
Beta-blocker			
baseline (%)	66.6	69.6	0.73
follow up (%)	70.8	63.1	0.26
Calcium channel blocker			
baseline (%)	30.1	25.0	0.53
follow up (%)	33.3	33.9	0.94
ACE-I			
baseline (%)	25.3	37.5	0.15
follow up (%)	22.2	33.9	0.15
ARB			
baseline (%)	42.8	28.5	0.10
follow up (%)	50.7	39.2	0.21

ACE-I = angiotensin II co-enzyme, ARB = angiotensin II receptor blocker, DIANA = DIAbetes and diffuse coronary Narrowing, DM = diabetes mellitus, IGT = impaired glucose tolerance, MI = myocardial infarction, PAD = peripheral arterial disease

categorical variables. The subjects' baseline demographics, medical histories, baseline and follow-up biochemical data (glycemic parameters, lipid profiles, high-sensitivity C-reactive protein, adiponectin and blood pressure) and QCA measurements were compared between the groups. Two-sample *t*-tests were performed to assess normally distributed continuous variables, the Wilcoxon rank-sum test was used to assess non-normally distributed continuous variables and the chi-square test was conducted to evaluate categorical variables. Univariate and multivariate analyses were performed to investigate clinical factors contributing to substantial atheroma progression. For the

univariate analysis, the following clinical variables and risk factors were regarded as covariates: age, glycemic status at baseline, % change in glucose, insulin, lipids, blood pressure, BMI, adiponectin and hs-CRP, baseline TLL and the use of cardiovascular medications and lifestyle interventions. We performed a multivariate logistic regression analysis based on the results of the univariate analysis. Model 1 of the multivariate analysis included all covariates with a *p*-value of <0.05 in the univariate analysis, as well as age and gender. Model 2 included the variables in Model 1 in addition to baseline LDL cholesterol, HbA1c and systolic blood pressure (SBP). A two-sided probability value of

Table 2. Risk Factor Control in the Progressors and Nonprogressors

	Non-progressor (<i>n</i> = 73)	Progressor (<i>n</i> = 64)	<i>p</i> -value
Glycemic Profile			
Fasting plasma glucose			
Baseline (mg/dL)	97.6 ± 10.2	97.6 ± 12.1	0.99
Follow-up (mg/dL)	99.8 ± 10.4	99.7 ± 13.3	0.97
Percent change (%)	+ 2.3 ± 10.9	+ 3.6 ± 17.4	0.63
Postprandial glucose			
Baseline (mg/dL)	196.5 ± 33.7	200.7 ± 35.5	0.50
Follow-up (mg/dL)	131.7 ± 36.4	136.3 ± 33.9	0.49
Percent change (%)	- 30.9 ± 16.6	- 34.9 ± 12.4	0.20
Fasting plasma insulin			
Baseline (IU/L)	7.2 ± 4.0	7.6 ± 5.4	0.69
Follow-up (IU/L)	6.8 ± 4.8	8.0 ± 6.7	0.27
Percent change (%)	+ 2.8 ± 45.4	+ 17.3 ± 69.2	0.21
Postprandial plasma insulin			
Baseline (IU/L)	126.0 ± 88.0	99.9 ± 58.6	0.07
Follow-up (IU/L)	65.3 ± 56.6	72.5 ± 53.4	0.50
Percent change (%)	- 34.5 ± 54.4	- 21.1 ± 45.4	0.19
HbA1c			
Baseline (%)	5.4 ± 0.4	5.5 ± 0.4	0.41
Follow-up (%)	5.3 ± 0.4	5.4 ± 0.3	0.57
Absolute change	- 0.08 ± 0.31	- 0.08 ± 0.35	0.98
Lipid Profile			
total cholesterol			
Baseline (mg/dL)	186.5 ± 37.0	190.7 ± 38.3	0.54
Follow-up (mg/dL)	170.2 ± 29.4	168.2 ± 31.2	0.71
Percent change (%)	- 6.4 ± 18.3	- 9.3 ± 20.2	0.41
triglyceride			
Baseline (mg/dL)	123.0 (96.0, 175.0)	135.0 (90.2, 204.0)	0.16
Follow-up (mg/dL)	110.0 (75.0, 158.0)	116.5 (89.5, 160.2)	0.08
Percent change (%)	- 5.8 ± 49.5	+ 11.2 ± 80.5	0.16
HDL-C			
Baseline (mg/dL)	42.4 ± 10.8	40.0 ± 8.9	0.19
Follow-up (mg/dL)	48.9 ± 11.4	47.1 ± 10.8	0.40
Percent change (%)	+ 18.5 ± 28.1	+ 21.7 ± 37.9	0.60
LDL-C			
Baseline (mg/dL)	119.3 ± 30.8	124.3 ± 33.2	0.39
Follow-up (mg/dL)	100.8 ± 25.3	96.9 ± 24.1	0.39
Percent change (%)	- 10.9 ± 27.3	- 17.1 ± 26.4	0.21
Blood Pressure			
SBP			
Baseline (mmHg)	125.0 ± 14.5	120.3 ± 12.6	0.06
Follow-up (mmHg)	124.4 ± 16.6	126.2 ± 13.9	0.52
Percent change (%)	- 1.8 ± 17.1	+ 5.4 ± 10.9	0.007
DBP			
Baseline (mmHg)	69.4 ± 9.3	69.3 ± 8.9	0.94
Follow-up (mmHg)	69.3 ± 10.3	71.5 ± 10.3	0.24
Percent change (%)	- 0.7 ± 20.7	+ 4.0 ± 14.9	0.15

(Cont Table 2)

	Non-progressor (<i>n</i> = 73)	Progressor (<i>n</i> = 64)	<i>p</i> -value
Others			
BMI			
Baseline (kg/m ²)	24.1 ± 2.8	24.4 ± 3.2	0.61
Follow-up (kg/m ²)	23.7 ± 3.1	24.1 ± 3.3	0.51
Percent change (%)	− 1.3 ± 6.4	− 0.8 ± 7.6	0.67
Adiponectin			
Baseline (mg/L)	7.3 ± 4.0	7.3 ± 3.1	0.96
Follow-up (mg/L)	8.7 ± 3.5	8.9 ± 3.9	0.75
Percent change (%)	+ 26.6 ± 34.6	+ 23.5 ± 45.4	0.71
Hs-CRP			
Baseline (mg/dL)*	3.9 (1.4, 9.1)	2.8 (0.7, 7.5)	0.08
Follow-up (mg/dL)*	0.7 (0.3, 2.6)	0.5 (0.2, 1.4)	0.91
Percent change (%)	− 81.1 ± 32.4	− 82.1 ± 28.6	0.90

The values are presented as the mean ± SD or median (interquartile range).

BMI = body mass index, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HMW = high molecular weight, Hs-CRP = high-sensitivity c-reactive protein, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure

*: Median (interquartile range)

<0.05 was considered to be statistically significant. All analyses were performed using the JMP software program, version 8.0.2 (SAS Institute, Cary, North Carolina).

Results

Clinical Demographics of the Study Subjects

In the current study, 46% (*n* = 64) of the study participants exhibited substantial atheroma progression at one year despite improvements in glycemic abnormalities. The clinical characteristics of the progressors and non-progressors are summarized in **Table 1**. The study subjects were predominantly men (86.0%), with a high prevalence of hypertension (85.9%) and dyslipidemia (66.6%). The use of various antiatherosclerotic medications and the assigned antidiabetic therapy at baseline and one year were identical between the two groups.

Risk Factor Control

The degree of risk factor control is summarized in **Table 2**. At baseline, the values of each risk factor were comparable. At one year, despite the use of various antihypertensive therapies (beta-blockers: 63.1%, calcium channel blockers: 33.9%, angiotensin II co-enzyme inhibitors: 33.9%, angiotensin II receptor blockers: 39.2%), the progressors exhibited increased SBP values (percent change: + 5.4 ± 10.9% vs. − 1.8 ±

17.1%, *p* = 0.007). The glycemic and lipid profiles and other biomarkers were similar between the two groups.

Measurements of the Atheroma Burden on Angiography

The measurements of the atheroma burden at baseline and on the serial evaluations are summarized in **Table 3**. The progressors demonstrated less extensive disease at baseline, as reflected by a shorter TLL (10.1 ± 9.8 mm vs. 14.4 ± 11.2 mm, *p* = 0.01). Predictably, profound atheroma progression was observed in the progressors, with a greater absolute (+ 4.3 ± 2.8 mm vs. − 2.1 ± 2.7 mm, *p* < 0.0001) and percent change in TLL (+ 41.0 ± 39.9% vs. − 15.9 ± 16.8%, *p* < 0.0001).

Independent Predictors of Disease Progression Despite Optimal Glucose Control

The results of the univariate and multivariate analyses of the predictors of disease progression are summarized in **Table 4**. The multivariate analysis demonstrated that an increased SBP (*p* = 0.001), treatment without statins at follow-up (*p* = 0.03) and the baseline TLL (*p* = 0.005) were associated with disease progression (**Table 4**, Model 1). In addition, even after adjusting for age, gender, baseline LDL-cholesterol (LDL-C), HbA1c and SBP, the analysis continued to show that independently associated risk factors for atheroma progression in early-stage diabetic

Table 3. Measurements of the Atheroma Burden in the Progressors and Nonprogressors

	Non-progressor (<i>n</i> = 73)	Progressor (<i>n</i> = 64)	<i>p</i> -value
Baseline TLL (mm)	14.4 ± 11.2	10.1 ± 9.8	0.01
One-year TLL (mm)	12.2 ± 10.3	15.0 ± 13.7	0.21
Absolute change from baseline (mm)	− 2.1 ± 2.7	+ 4.3 ± 2.8	< 0.0001
% change from baseline	− 15.9 ± 16.8	41.0 ± 39.9	< 0.0001

TLL = total lesion length

patients with optimal glucose control included an increased SBP ($p=0.006$), treatment without statins at follow-up ($p=0.03$) and the baseline TLL ($p=0.007$) (Table 4, Model 2).

Discussion

The findings of the DIANA study illustrated the importance of achieving glycemic control for preventing atheroma progression in early-stage diabetic patients with CAD¹³. However, the current subanalysis demonstrated that 46% of the patients with an improved glycemic status continued to exhibit disease progression. Furthermore, the patients with greater increases in SBP and those who did not receive statin therapy were more likely to demonstrate disease progression. Our findings suggest the importance of providing blood pressure treatment and statin therapy, in addition to glucose-lowering treatment, for preventing the progression of coronary atherosclerosis in early-stage diabetic patients.

Previous studies have reported the benefits of pharmacological and lifestyle interventions in improving the glycemic status and/or future outcomes in patients with prediabetes or newly diagnosed diabetes^{16–18}. Additionally, the DIANA study demonstrated the antiatherosclerotic efficacy of early glucose modification therapy in patients with early-stage diabetes¹³. However, there is a paucity of data regarding early-stage diabetic patients who subsequently experience cardiovascular events or progression of atherosclerotic disease despite exhibiting a well-controlled glycemic status.

In the current analysis, achieving improvements in abnormal glycemic tolerance did not halt the progression of atheroma in 46% of the study subjects in the DIANA study. Since residual risk factors contribute to atheroma progression, our observations support the concept that coronary atherosclerosis is a multifactorial disease that requires a therapeutic approach to modify global risks rather than individual risk factors in order to prevent disease progression. These findings

are supported by the results of previous clinical studies of advanced diabetic patients. The Steno-II study demonstrated the benefits of multifactorial intensified intervention for preventing future cardiovascular events¹⁹. The PERISCOPE (Comparison of Pioglitazone Versus Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes) trial illustrated the antiatherosclerotic benefits of pioglitazone in modifying glycemic as well as non-glycemic factors²⁰. In addition, the use of strategies to control multiple risks is crucial for preventing cardiovascular disease, even among Japanese diabetic patients with a relatively lower incidence of CAD²¹. As diabetes promotes the development of atherosclerosis in the setting of profound metabolic abnormalities, including hypertension, dyslipidemia and increased systemic inflammation^{22–25}, the current results highlight the significance of global risk management, even early-stage diabetic patients, for preventing disease progression.

Our findings indicate that relatively a small increase in SBP is associated with substantial atheroma progression. Interestingly, although the observed small rise in SBP remained within the normal blood pressure range, the progression of coronary atherosclerosis was substantial. Considering that atherosclerotic plaque accumulates and vascular risks begin to increase when the blood pressure exceeds 115/75 mmHg^{26, 27}, obtaining lower blood pressure values is crucial for modifying the progressive nature of the disease in early-stage diabetics. Further investigation to clarify the optimal SBP goal in this population is required.

Large randomized clinical trials have consistently demonstrated the antiatherosclerotic benefits of statins in various subjects, including diabetic patients^{28–31}. The current study also highlights the importance of statin use in early-stage diabetics with CAD. Inflammation and oxidative stress are believed to be drivers contributing to disease progression in diabetic patients^{32, 33}. Given that statins modulate pathways of inflammation and oxidation^{34, 35}, statin-mediated pleiotropic effects may result in reduced progression of coronary

Table 4. Clinical Predictors of Atheroma Progression

(a) Univariate Analysis		
	Odds ratio (95% CI)	<i>p</i> -value
Age	1.017 (0.979-1.057)	0.24
Female	2.401 (0.825-7.992)	0.11
diagnosis of IGT at baseline	1.364 (0.663-2.824)	0.39
% change in Fasting plasma glucose	0.993 (0.967-1.019)	0.62
% change in Postprandial glucose	1.001 (0.976-1.026)	0.91
% change in Fasting plasma insulin	0.995 (0.988-1.002)	0.20
% change in Postprandial plasma insulin	0.994 (0.985-1.002)	0.18
change in HbA1c	0.992 (0.325-3.010)	0.98
% change in total cholesterol	1.007 (0.989-1.027)	0.41
% change in triglyceride	0.995 (0.989-1.001)	0.15
% change in HDL cholesterol	0.997 (0.985-1.011)	0.70
% change in LDL cholesterol	1.008 (0.995-1.023)	0.20
% change in SBP	1.067 (1.026-1.136)	0.003
% change in DBP	0.984 (0.962-1.005)	0.14
% change in BMI	0.988 (0.937-1.041)	0.66
% change in adiponectin	1.002 (0.991-1.013)	0.71
% change in hs-CRP	0.999 (0.998-1.001)	0.29
Statin use at one year	0.533 (0.198-0.941)	0.03
Beta-blocker at one year	1.425 (0.458-2.811)	0.26
Calcium channel blocker at one year	0.973 (0.453-2.095)	0.94
ACE-I at one year	0.556 (0.243-1.245)	0.15
ARB at one year	1.595 (0.772-3.334)	0.20
Life-style intervention	0.724 (0.461-1.593)	0.49
Baseline TLL	0.614 (0.218-0.905)	0.001

ACE-I=angiotensin II coenzyme inhibitor, ARB=angiotensin II receptor blocker, DBP=diastolic blood pressure, HbA1c=glycated hemoglobin, HDL=high-density lipoprotein, hs-CRP=high-sensitivity c-reactive protein, IGT=impaired glucose tolerance, LDL=low-density lipoprotein, SBP=systolic blood pressure, TLL=total lesion length

(b) Multivariate Analysis**Model 1***

	Odds ratio (95% CI)	<i>p</i> -value
Age	1.010 (0.969-1.052)	0.63
Female	2.706 (0.845-10.027)	0.09
% change in SBP	1.053 (1.019-1.087)	0.001
Statin use at one year	0.357 (0.120-0.977)	0.03
Baseline TLL	0.738 (0.222-0.933)	0.005

* Model 1 includes covariates with a *p*-value of <0.05 in the univariate analysis, as well as age and gender.

Model 2[#]

	Odds ratio (95% CI)	<i>p</i> -value
Age	1.007 (0.964-1.053)	0.72
Female	1.572 (0.318-6.083)	0.43
Baseline LDL cholesterol	0.993 (0.980-1.006)	0.33
Baseline HbA1c	0.656 (0.243-1.728)	0.39
Baseline SBP	1.014 (0.981-1.051)	0.39
% change in SBP	1.046 (1.012-1.083)	0.006
Statin use at one year	0.417 (0.139-0.936)	0.03
Baseline TLL	0.754 (0.231-0.952)	0.007

[#] Model 2 includes the variables in Model 1 in addition to baseline LDL cholesterol, HbA1c and SBP. HbA1c=glycated hemoglobin, LDL=low-density lipoprotein, SBP=systolic blood pressure, TLL=total lesion length

atherosclerosis in early-stage diabetics with CAD.

The presence of ongoing disease progression despite the achievement of an LDL-C level below 100 mg/dL in the progressors indicates the need for stricter control of LDL-C, even in early-stage diabetics with CAD. Recent studies have demonstrated that coronary atherosclerosis regresses if a very low level of LDL-C is achieved with potent statin therapy^{36, 37)}. As statin use was found to be a significant factor associated with reduced disease progression in early-stage diabetics with CAD in this study, the optimal dose of statin therapy and target level of LDL-C in such patients should be clarified in future studies.

A number of caveats regarding the present study should be noted. This post hoc analysis evaluated observational data generated from the DIANA study. The study population was relatively small, and the study lacked sufficient power to examine the association between plaque progression and outcomes. As all patients had a diagnosis of CAD, it is unknown if the current findings can be translated to the setting of primary prevention. However, the observation that asymptomatic diabetic patients have prospective cardiovascular risks comparable to those of nondiabetic survivors of myocardial infarction³⁸⁾ suggests that the underlying disease is aggressive, even among patients who have yet to receive clinical attention. Coronary angiography has limitations in evaluating plaque composition and vessel remodeling. While the features observed on this modality have been reported to be associated with disease progression, plaque vulnerability and cardiovascular events^{39, 40)}, it remains to be determined whether progressors are different from non-progressors with regard to plaque composition and vessel remodeling. Given that recent intravascular imaging modalities enable clinicians to visualize morphology, it would be interesting to investigate the characteristics of plaque in progressors and non-progressors using serial intravascular imaging.

In summary, despite exhibiting favorable control of their glycemic status, 46% of the early-stage diabetic patients with CAD evaluated in this study continued to demonstrate atheroma progression. Additionally, the greatest antiatherosclerotic impact is likely to be achieved under SBP control and treatment with statins. These findings intensify the clinical need to adopt a therapeutic strategy for modifying multiple risk factors in order to halt disease progression in early-stage diabetic patients with CAD.

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Conflicts of Interest

None.

Abbreviations

CAD=coronary artery disease, DIANA=DIAbetes and diffuse coronary NArrowing, DM=diabetes mellitus, HbA1c=glycosylated hemoglobin, HDL=high-density lipoprotein, IGT=impaired glucose tolerance, LDL=low-density lipoprotein, OGTT=oral glucose tolerance test, SBP=systolic blood pressure, TLL=total lesion length, QCA=quantitative coronary angiography.

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