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Ⅴ．資料

Original Article

Small Dense Low-Density Lipoproteins Cholesterol can Predict Incident Cardiovascular Disease in an Urban Japanese Cohort: The Suita Study

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Aim: **Several lines of evidence indicate that small dense low-density lipoproteins (sd-LDL) are more atherogenic than large buoyant LDL; however, few prospective studies have addressed the role of sd-LDL in cardiovascular disease (CVD). We therefore examined the association between sd-LDL cholesterol (sd-LDL-C) and CVD in a Japanese cohort.**

Methods: **An 11.7-year prospective study was performed using a general population aged 30-79 without a history of cardiovascular disease. Direct LDL-C and sd-LDL-C were measured in samples from 2034 participants (968 men and 1066 women).**

Results: **During the follow-up period, there were 116 incident cases of CVD. The multivariable-adjusted hazard ratios (HRs) of sd-LDL-C for CVD were calculated using a proportional hazards regression model after adjusting for age, hypertension, diabetes, use of lipid-lowering drugs, body mass index, and current smoking and alcohol drinking, and found that increasing quartiles of sd-LDL-C were associated with increased risk of CVD. We also determined that age and sex-adjusted HRs per 10 mg/dL of sd-LDL-C and HRs for CVD, stroke, cerebral infarction, and coronary artery disease were 1.21 (95% CI: 1.12-1.31), 1.17 (95% CI: 1.05-1.30), 1.15 (95% CI: 1.00-1.33), and 1.29 (95% CI: 1.14-1.45), respectively.**

Conclusions: **It was demonstrated that sd-LDL-C was significantly associated with CVD in a Japanese population, providing evidence of sd-LDL-C as an important biomarker to predict CVD.**

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Key words; Cardiovascular disease, Lipoproteins, Lipids, Risk factors, Epidemiology

Introduction

The causal relationship between high levels of serum low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD) has been well established in previous cohort studies[1-5]. Recent clinical trials have also indicated significant event reduction by statins in the primary and secondary prevention of CVD[6-8]; therefore, LDL-C is one of the most important risk factors of CVD and many guidelines, including ours, recommend certain target LDL-C goals for risk management to prevent the development of CVD[5].

Although we use LDL-C as the primary target for cholesterol-lowering therapy, LDL particles are heterogeneous with respect to size and density. Compared to large, buoyant LDL, small dense LDL (sd-LDL) particles exhibit a prolonged plasma residence time, increased penetration into the arterial wall, lower affinity for the LDL receptor, and increased sus-

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ceptibility to oxidation[9]. Thus, sd-LDL particles possess elevated atherogenic potential. Furthermore, elevated concentrations of sd-LDL can be found in patients with type 2 diabetes, metabolic syndrome, chronic kidney disease, and familial combined hyperlipidemia[10-14], all of which have been found as highly atherogenic conditions. Although Hirano *et al.* showed that sd-LDL-C is significantly higher in patients with coronary artery disease (CAD) in a cross-sectional study[14], no prospective study has addressed whether sd-LDL-C can predict a risk for CVD in non-Western populations. Recently, the Québec Cardiovascular Study has shown prospectively that men with an elevated proportion of LDL with a diameter less than 25.5 nm had a 3.6-fold increased risk of CAD compared with men with relatively normal LDL[15], indicating the strong link of sd-LDL to CVD as a biomarker of cardiovascular disease. Due to its atherogenic properties it is useful to measure sd-LDL for risk assessment; however, a reliable routine method is lacking.

sd-LDL has been measured by ultracentrifugation[16] or gradient gel electrophoresis[17]; however, these methods are both unsuitable for routine analysis, because each requires expensive equipment, complicated techniques, and long assay times. Hirano *et al.* have recently developed a simple precipitation method for sd-LDL-C quantification consisting of 2 steps: removal of apolipoprotein B-containing sd-LDL-free lipoproteins by precipitation with heparin and magnesium, followed by LDL-C measurement by the homogeneous method[18, 19]. This assay allowed us to screen sd-LDL-C in a large cohort. Using this assay, Ai *et al.* recently performed a case control study using samples from the Framingham Offspring Study and found significantly higher sd-LDL-C in women with CAD[20]. Koba *et al.* also showed that sd-LDL-C is more powerful than LDL-C for the determination of CAD[21]; however, these are cross-sectional studies and a prospective study is required to determine whether sd-LDL is an independent predictor of CVD. Therefore, the aim of this study was to address the role of sd-LDL-C for incident CVD in a large cohort study in Japan, the Suita study.

Methods

Population

The Suita study, a cohort study on CVD of urban residents, was established in 1989. The details of this study have been described elsewhere[22]. Briefly, 6485 men and women aged 30-79 years underwent a baseline survey at the National Cerebral and Cardiovascular Center between September 1989 and March 1994, and received medical examinations every 2 years. For these participants, we set the baseline of the present study at medical examinations held between April 1994 and February 1995, since at that time serum samples were collected and stored at −80℃. During this period, 2,437 participants attended the medical examination and were followed until the end of 2007. Of these, 403 participants were excluded due to the following reasons: history of CAD or stroke (n=106), lost to follow-up (n=132), and other reasons such as missing data (n=165). Data from the remaining 2,034 participants (968 men and 1,066 women) were included in the analysis. Informed consent was obtained from all participants. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline Examination

Blood samples were collected after the participants had fasted for at least 10 hours. The samples were centrifuged immediately. Blood pressure was measured in triplicate on the right arm after 5 min of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for analysis. At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP < 120 mmHg and DBP < 80 mmHg), normal (SBP 120-129 mmHg or DBP 80-84 mmHg), high-normal blood pressure (SBP 130-139 mmHg or DBP 85-89 mmHg), hypertension grade 1 (SBP 140-159 mmHg or DBP 90-99 mmHg), or hypertension grade ≥2 (SBP ≥160 mmHg or DBP ≥100 mmHg). Antihypertensive drug users were classified according to their blood pressure at the baseline survey. Diabetes was defined as fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or current use of medications for diabetes. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Well-trained health nurses obtained information on smoking, drinking, and medical histories.

Laboratory Measurements

Serum total cholesterol, triglyceride, and HDL cholesterol (HDL-C) were determined by standard enzymatic methods. Serum glucose was also measured. For the purposes of this study, we used archived plasma samples that had been frozen at −80℃ and never previously thawed for the assessment of direct LDL-C and sd-LDL-C by homogeneous methods on a Hitachi 7180 automated analyzer (Hitachi, Tokyo, Japan)[18, 19]. The kits used for these tests (LDL-C and sd-LDL-C) were provided by Denka Seiken (Tokyo, Japan). Assays

for direct LDL-C and sd-LDL-C were previously calibrated and directly compared with concentrations obtained after isolation of LDL and sd-LDL by ultracentrifugation.

Endpoint Determination

As previously reported, the endpoints of the present study were (1) date of first CAD or stroke event; (2) date of death; (3) date of leaving Suita city; and (4) the end of December 2007. The first step in the survey for CAD and stroke involved checking the health status of all participants by repeated clinical visits every two years and yearly questionnaires by mail or telephone. In the second step, in-hospital medical records of participants who were suspected of having CAD were reviewed by registered hospital physicians or research physicians who were blinded to the baseline information. The criteria for a diagnosis of CAD included first-ever acute myocardial infarction, sudden cardiac death within 24 h after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project[23]. The criteria for stroke were defined according to the US National Survey of Stroke criteria[24]. Classification of patients into stroke subtypes was based on examination of computed tomography, magnetic resonance imaging, or autopsy.

Statistical Analysis

Continuous variables between groups were compared by analysis of variance and categorical variables were compared by a chi-square test. Triglyceride levels were logarithmically transformed to improve the skewed distribution. The hazard ratio (HR) for MI or stroke was calculated using a proportional hazards model adjusted for age, sex, hypertension (dichotomous variable), diabetes, HDL-C, BMI, smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker). All confidence intervals were estimated at the 95% level and significance was set at $p<0.05$. All statistical analyses were conducted using the SAS statistical software package (release version 8.2; SAS Institute, Cary, NC, USA).

Results

Baseline Clinical Characteristics According to sd-LDL-C Quartiles

To study the role of sd-LDL in the incidence of CVD, we divided the cohort into quartiles according to the basal level of sd-LDL-C. **Table 1** shows the clinical characteristics and cardiovascular risk factors of the study population according to the quartiles of sd-LDL-C. BMI, total cholesterol, LDL-C, and triglyceride significantly increased across the sd-LDL-C quartiles both in men and women, while HDL-C decreased in both genders. A significant trend was observed across the quartiles for the severity of high blood pressure, lipid-lowering drug use, and prevalence of diabetes at baseline both in men and women; however, a significant trend for age was only found in women, not in men.

Incidence of CVD According to sd-LDL-C Quartiles

To confirm our previous study, the association between LDL-C and CAD was examined by dividing the cohort into quartiles according to the baseline LDL-C. It was found that age- and multivariable-adjusted HRs for CAD were statistically significant only in men, not in women or the total cohort. The HR of the 4th quartile in men was 3.53 (95% confidence intervals (CIs): 1.31-9.54) in an age-adjusted model and 3.56 (95% CIs: 1.28-9.86) in a multivariable-adjusted model, consistent with our previous report[1]. We then performed analysis to examine the effect of sd-LDL-C. During the observation period, 116 cases of CVD, 53 cases of stroke, 36 cases of cerebral infarction, and 63 cases of CAD were reported. As shown in **Table 2**, increasing quartiles of sd-LDL-C were significantly associated with increased risks of CVD (stroke + CAD), stroke, cerebral infarction, and CAD after age and multivariable adjustment. Age and sex-adjusted HRs per 10 mg/dL of sd-LDL-C for CVD, stroke, cerebral infarction, and CAD were 1.21 (95% CI: 1.12-1.31), 1.17 (95% CI: 1.05-1.30), 1.15 (95% CI: 1.00-1.33), and 1.29 (95% CI: 1.14-1.45), respectively. HRs after multivariable adjustment were almost the same. When we analyzed each gender, age-adjusted HRs per 10 mg/dL of sd-LDL-C for CVD, stroke, cerebral infarction, and CAD were significant in women, while those for CVD and CAD were significant in men. HR for CAD of the fourth quartile was almost 4 after age and multivariable adjustment in men.

After putting LDL-C into the multivariable adjusted-models (Model A), sd-LDL-C was still associated with increased risk for CVD, stroke, cerebral infarction, and CAD in the total cohort, for CVD in men, and CVD, stroke, and cerebral infarction in women. After further putting logarithmically transformed triglyceride and HDL-C variables into Model A (Model B), sd-LDL-C was still associated with

Table 1. Baseline characteristics of cardiovascular risk factors according to small dense LDL cholesterol quartiles

	Small dense LDL Cholesterol				*p* value for Trend
	Q1	Q2	Q3	Q4	
Men					
Number of subjects	241	243	242	242	
Small dense LDL, range (mean), mg/dL	6.3-27.8 (21.1)	27.9-38.2 (32.7)	38.3-53.4 (45.3)	53.5-119.6 (67.3)	
Age, year	60.9 ± 13.1	59.7 ± 12.5	59.1 ± 12.3	59.4 ± 11.3	0.421
Body mass index, kg/m^2	21.5 ± 2.5	22.4 ± 2.8	23.4 ± 2.4	24.0 ± 2.7	<0.001
TC, mg/dL	170 ± 25	189 ± 24	199 ± 25	220 ± 27	<0.001
HDL-C, mg/dL	60 ± 15	57 ± 14	51 ± 11	48 ± 11	<0.001
LDL-C, mg/dL	86 ± 20	111 ± 21	124 ± 23	140 ± 26	<0.001
Triglyceride, (median) mg/dL	66	87	112	167	<0.001
Large-LDL-C, mg/dL	65 ± 17	78 ± 21	79 ± 22	72 ± 24	<0.001
Sd-LDL-C/LDL-C ratio	0.25 ± 0.05	0.31 ± 0.07	0.38 ± 0.08	0.50 ± 0.11	<0.001
Blood pressure category, %					0.002
Optimal blood pressure	31	26	25	19	
Normal blood pressure	30	24	19	26	
High-normal blood pressure	16	30	25	29	
Hypertension grade 1-3	19	26	29	28	
Antilipidemic drug use, %	1	4	5	8	0.003
Diabetes, %	3	5	7	9	0.023
Current Smoking, %	44	41	41	44	0.021
Current Drinking, %	66	71	72	74	0.577
Women					
Number of subjects	266	267	266	267	
Small dense LDL, range (mean), mg/dL	7.5-23.9 (18.7)	24.0-33.0 (28.6)	33.1-44.6 (38.5)	44.7-136.6 (59.7)	
Age, year	51.7 ± 13.0	57.3 ± 11.9	60.2 ± 11.2	60.4 ± 9.1	<0.001
Body mass index, kg/m^2	21.0 ± 2.5	21.8 ± 3.2	22.5 ± 3.1	23.2 ± 2.8	<0.001
TC, mg/dL	175 ± 23	200 ± 22	216 ± 25	234 ± 32	<0.001
HDL-C, mg/dL	67 ± 13	64 ± 12	60 ± 13	54 ± 12	<0.001
LDL-C, mg/dL	83 ± 17	109 ± 17	130 ± 18	153 ± 30	<0.001
Triglyceride, (median) mg/dL	61	78	97	140	<0.001
Large-LDL-C, mg/dL	64 ± 14	81 ± 15	92 ± 17	93 ± 25	<0.001
Sd-LDL-C/LDL-C ratio	0.23 ± 0.04	0.27 ± 0.04	0.30 ± 0.05	0.40 ± 0.08	<0.001
Blood pressure category, %					<0.001
Optimal blood pressure	34	27	22	17	
Normal blood pressure	25	24	26	25	
High-normal blood pressure	16	29	20	35	
Hypertension grade 1-3	16	21	31	32	
Antilipidemic drug use, %	4	5	6	12	0.002
Diabetes, %	0	1	3	6	<0.001
Current Smoking, %	13	10	6	7	0.056
Current Drinking, %	34	30	22	23	0.014

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Large LDL-C, LDL-C-Sd-LDL-C. Hypertension was defined as described in methods. Diabetes was defined as fasting serum glucose ≥7.0mmol/L (126 mg/dL), the use of antidiabetic agents, or both.

Table 2. Age- and multivariable-adjusted hazard ratios and 95% confidence intervals for the incidence of cardiovascular disease according to small dense LDL cholesterol quartiles

	Small dense LDL Cholesterol, mg/dL				
	Q1 (Lower)	Q2	Q3	Q4 (Higher)	per 10 mg/dL
Men and women, range (mean)	6.3-25.5 (19.7)	25.6-35.3 (30.5)	35.4-49.0 (41.4)	49.1-136.6 (63.9)	
Person-years	5,576	5,789	5,527	5,741	
Cardiovascular disease					
Case	21	23	29	43	
Age and sex-adjusted HR	1	0.75 (0.43-1.29)	1.11 (0.68-1.83)	**1.64 (1.04-2.60)**	**1.21 (1.12-1.31)**
Model 1-adjusted HR	1	0.81 (0.45-1.42)	1.08 (0.65-1.81)	1.60 (0.99-2.60)	**1.21 (1.11-1.32)**
Stroke					
Case	14	13	10	16	
Age and sex-adjusted HR	1	0.58 (0.30-1.14)	0.80 (0.43-1.48)	1.21 (0.69-2.12)	**1.17 (1.05-1.30)**
Model 1-adjusted HR	1	0.63 (0.32-1.23)	0.79 (0.41-1.50)	1.19 (0.65-2.16)	**1.18 (1.04-1.33)**
Cerebral infarction					
Case	8	10	6	12	
Age and sex-adjusted HR	1	1.08 (0.45-2.57)	1.14 (0.47-2.73)	1.74 (0.77-3.90)	**1.15 (1.00-1.33)**
Model 1-adjusted HR	1	1.18 (0.48-2.88)	1.16 (0.46-2.89)	1.85 (0.77-4.40)	**1.18 (1.00-1.39)**
Coronary artery disease					
Case	7	10	19	27	
Age and sex-adjusted HR	1	1.36 (0.49-3.77)	2.26 (0.89-5.73)	**3.35 (1.38-8.13)**	**1.29 (1.14-1.45)**
Model 1-adjusted HR	1	1.44 (0.51-4.08)	2.17 (0.83-5.66)	**3.26 (1.29-8.20)**	**1.28 (1.13-1.46)**
Men, range (mean)	6.3-27.8 (21.1)	27.9-38.2 (32.7)	38.3-53.4 (45.3)	53.5-119.6 (67.3)	
Person-years	2,499	2,615	2,519	2,608	
Cardiovascular disease					
Case	19	19	22	36	
Age-adjusted HR	1	1.06 (0.56-2.01)	1.31 (0.70-2.44)	**2.03 (1.16-3.57)**	**1.15 (1.04-1.28)**
Model 1-adjusted HR	1	1.17 (0.61-2.24)	1.36 (0.70-2.62)	**2.12 (1.16-3.86)**	**1.16 (1.04-1.30)**
Stroke					
Case	14	13	10	16	
Age-adjusted HR	1	1.03 (0.48-2.21)	0.87 (0.38-1.99)	1.43 (0.69-2.97)	1.06 (0.92-1.23)
Model 1-adjusted HR	1	1.13 (0.51-2.47)	0.98 (0.40-2.38)	1.55 (0.70-3.41)	1.08 (0.92-1.28)
Cerebral infarction					
Case	8	10	6	12	
Age-adjusted HR	1	1.33 (0.52-3.39)	0.85 (0.29-2.48)	1.81 (0.73-4.48)	1.08 (0.91-1.29)
Model 1-adjusted HR	1	1.43 (0.54-3.78)	0.90 (0.29-2.80)	1.93 (0.70-5.29)	1.10 (0.90-1.36)
Coronary artery disease					
Case	5	6	12	20	
Age-adjusted HR	1	1.24 (0.37-4.07)	2.48 (0.87-7.07)	**3.89 (1.45-10.42)**	**1.27 (1.10-1.47)**
Model 1-adjusted HR	1	1.27 (0.38-4.29)	2.34 (0.78-6.97)	**4.03 (1.42-11.40)**	**1.28 (1.09-1.50)**
Women, range (mean)	7.5-23.9 (18.7)	24.0-33.0 (28.6)	33.1-44.6 (38.5)	44.7-136.6 (59.7)	
Person-years	3,077	3,174	3,008	3,133	
Cardiovascular disease					
Case	7	12	13	23	
Age-adjusted HR	1	1.01 (0.39-2.60)	0.99 (0.39-2.50)	1.73 (0.74-4.06)	**1.31 (1.16-1.47)**
Model 1-adjusted HR	1	1.04 (0.40-2.72)	0.91 (0.35-2.35)	1.52 (0.63-3.68)	**1.29 (1.13-1.48)**
Stroke					
Case	5	8	6	16	
Age-adjusted HR	1	0.95 (0.30-2.94)	0.64 (0.19-2.11)	1.72 (0.62-4.74)	**1.31 (1.13-1.52)**
Model 1-adjusted HR	1	0.98 (0.31-3.14)	0.64 (0.18-2.19)	1.66 (0.58-4.76)	**1.33 (1.12-1.59)**

(Cont Table 2)

	Small dense LDL Cholesterol, mg/dL				
	Q1 (Lower)	Q2	Q3	Q4 (Higher)	per 10 mg/dL
Cerebral infarction					
Case	0	5	4	7	
Age-adjusted HR	1	–	–	–	**1.31 (1.05-1.63)**
Model 1-adjusted HR	1	–	–	–	**1.37 (1.05-1.80)**
Coronary artery disease					
Case	2	4	7	7	
Age-adjusted HR	1	1.22 (0.22-7.76)	1.90 (0.39-9.24)	1.84 (0.38-8.91)	**1.32 (1.08-1.61)**
Model 1-adjusted HR	1	1.27 (0.22-7.33)	1.83 (0.35-9.45)	1.54 (0.30-7.83)	1.23 (0.99-1.53)

Model 1: adjusted for age, (sex), body mass index, smoking, drinking, blood pressure category (optimal, normal, and high-normal blood pressure, hypertension grade 1 and 2 + 3), diabetes, and lipid-lowering drug user
Bold numbers: statistically significant

increased risks of CVD and stroke in the total cohort and in women, but not in men (**Table 3**).

Discussion

This study clearly indicates an increased risk of CVD, stroke, cerebral infarction, and CAD attributed to elevated sd-LDL-C concentrations in a Japanese population without a previous history of CVD. We also showed that HR was significant after multivariable adjustment and by analysis including LDL-C, log-transformed triglyceride, and HDL-C in the same model. Thus, sd-LDL-C measurement with the new test is promising as a new biomarker to predict the risk of CVD.

In addition to traditional risk factors for CVD, such as hypertension, diabetes, and dyslipidemia, other biomarkers are required to better define the risk and refine therapeutic decisions. There is scientific evidence that sd-LDL particles are highly atherogenic and can be a biomarker of CVD[15, 20, 21]. Our data provide additional evidence to show the role of sd-LDL-C as a CVD risk in the general population. Furthermore, measuring sd-LDL-C with this test has an advantage because it is more user-friendly and more applicable than specialized tests such as gradient gel electrophoresis, nuclear magnetic resonance, and gradient ultracentrifugation.

Until now, there have been no target goals of sd-LDL-C to prevent CAD. In this study the HR of the 4th quartile was statistically significant, suggesting that the cutoff of sd-LDL-C is approximately 50 mg/dL, although significance was not obtained in women probably due to the low event rate; therefore, a larger study should be performed to define an appropriate cutoff for sd-LDL-C. Because statins, fibrates, and ezetimibe have been shown to reduce the amount of sd-LDL[25-28], a randomized control study is required to address whether lowering sd-LDL-C to a certain goal by these drugs can prevent the development of CAD.

In this study we found that sd-LDL-C was significantly associated with traditional risk factors, such as hypertension and diabetes. BMI and the prevalence of diabetes increased and HDL-C decreased across the sd-LDL-C quartiles, and more hypertensive subjects were found in second to fourth quartiles than in the first quartile in both genders. We also found that age-adjusted partial correlation coefficients between sd-LDL-C and BMI, log-transformed triglyceride, LDL-C, and HDL-C (Pearson) were 0.305, 0.636, 0.554, and −0.346 ($p<0.0001$), respectively. Thus these data suggest that increased concentrations of sd-LDL-C may be associated with metabolic disorders and that lifestyle modification, such as exercise and weight control, would be effective to reduce sd-LDL in patients with diabetes and metabolic syndrome. Furthermore, we should address whether sd-LDL-C can be used to identify a very high-risk patient with type 2 diabetes, metabolic syndrome, and other metabolic disorders. In contrast to the association with metabolic disorders, an age-related change in sd-LDL-C was found only in women, consistent with the trend of increased atherogenic dyslipidemia in postmenopausal women. Ai *et al.* also found that postmenopausal women had higher levels of sd-LDL-C than premenopausal women in the Framingham Offspring Study[20].

In addition to type 2 diabetes and metabolic syn-

Table 3. Relationship between major lipid variables and cardiovascular disease

	Cardiovascular disase	Stroke	Cerebral infarction	Coronary artery disease
Men and women				
Age and sex-adjusted	**1.21 (1.12-1.31)**	**1.17 (1.05-1.30)**	**1.15 (1.00-1.33)**	**1.29 (1.14-1.45)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.21 (1.11-1.32)**	**1.18 (1.04-1.33)**	**1.18 (1.00-1.39)**	**1.28 (1.13-1.46)**
Model A				
Sd-LDL-C/10 mg/dL	**1.26 (1.11-1.43)**	**1.26 (1.06-1.50)**	**1.29 (1.02-1.62)**	**1.29 (1.07-1.55)**
LDL-C/10 mg/dL	0.96 (0.89-1.04)	0.94 (0.85-1.04)	0.93 (0.81-1.06)	0.99 (0.88-1.11)
Model B				
Sd-LDL-C/10 mg/dL	**1.20 (1.01-1.42)**	**1.35 (1.07-1.71)**	1.31 (0.96-1.78)	1.05 (0.81-1.36)
LDL-C/10 mg/dL	0.98 (0.90-1.06)	0.93 (0.83-1.03)	0.92 (0.80-1.07)	1.05 (0.93-1.19)
ln_TG	1.15 (0.71-1.86)	0.76 (0.40-1.46)	0.86 (0.37-1.96)	1.82 (0.87-3.81)
HDL-C/10 mg/dL	0.94 (0.81-1.08)	1.00 (0.84-1.20)	0.93 (0.73-1.18)	0.80 (0.61-1.04)
Men				
Age-adjusted	**1.15 (1.04-1.28)**	1.06 (0.92-1.23)	1.08 (0.91-1.29)	**1.27 (1.10-1.47)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.16 (1.04-1.30)**	1.08 (0.92-1.28)	1.10 (0.90-1.36)	**1.28 (1.09-1.50)**
Model A				
Sd-LDL-C/10 mg/dL	**1.17 (1.00-1.38)**	1.17 (0.92-1.48)	1.20 (0.90-1.60)	1.18 (0.94-1.48)
LDL-C/10 mg/dL	0.99 (0.89-1.09)	0.94 (0.82-1.08)	0.93 (0.79-1.09)	1.07 (0.93-1.24)
Model B				
Sd-LDL-C/10 mg/dL	1.10 (0.88-1.38)	1.28 (0.92-1.77)	1.28 (0.87-1.90)	0.96 (0.70-1.31)
LDL-C/10 mg/dL	1.01 (0.90-1.13)	0.92 (0.78-1.07)	0.91 (0.76-1.10)	1.14 (0.97-1.33)
ln_TG	1.23 (0.66-2.26)	0.75 (0.32-1.76)	0.86 (0.31-2.38)	1.87 (0.75-4.62)
HDL-C/10 mg/dL	0.96 (0.80-1.14)	1.05 (0.85-1.28)	1.08 (0.94-1.40)	0.72 (0.50-1.03)
Women				
Age-adjusted	**1.31 (1.16-1.47)**	**1.31 (1.13-1.52)**	**1.31 (1.05-1.63)**	**1.32 (1.08-1.61)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.29 (1.13-1.48)**	**1.33 (1.12-1.59)**	**1.37 (1.05-1.80)**	1.23 (0.99-1.53)
Model A				
Sd-LDL-C/10 mg/dL	**1.44 (1.17-1.77)**	**1.48 (1.13-1.94)**	**1.62 (1.08-2.43)**	1.33 (0.94-1.89)
LDL-C/10 mg/dL	0.92 (0.81-1.04)	0.92 (0.79-1.08)	0.88 (0.69-1.11)	0.94 (0.75-1.16)
Model B				
Sd-LDL-C/10 mg/dL	**1.35 (1.03-1.77)**	**1.47 (1.04-2.08)**	1.33 (0.78-2.29)	1.12 (0.70-1.79)
LDL-C/10 mg/dL	0.93 (0.81-1.07)	0.92 (0.78-1.09)	0.92 (0.72-1.19)	0.98 (0.78-1.24)
ln_TG	1.19 (0.53-2.69)	0.91 (0.31-2.68)	0.86 (0.17-4.25)	1.84 (0.47-7.15)
HDL-C/10 mg/dL	0.92 (0.72-1.19)	0.92 (0.67-1.26)	0.56 (0.31-1.00)	0.92 (0.60-1.41)

Multivariable adjusted for age, sex, body mass index, smoking, drinking, blood pressure category (optimal, normal, and high-normal bloodpressure, hypertension grade 1 and 2 + 3), diabetes, and antilipidemic drug user
Model A: sd-LDL-C per 10 mg/dL and LDL-C per 10 mg/dL in the same model
Model B: sd-LDL-C per 10 mg/dL, LDL-C per 10 mg/dL, ln(TG), and HDL-C per 10 mg/dL in the same model
Sd-LDL-C, small dense LDL cholesterol; ln_TG, logarithmical transformed TG
Bold numbers: statistically significant

drome, sd-LDL-C is increased in familial combined hyperlipidemia and postprandial hyperlipidemia[29, 30]. Hirano *et al.* demonstrated that sd-LDL-C determined by this simple precipitation method is useful for screening familial combined hyperlipidemia in large populations[13]. Because the prevalence of familial combined hyperlipidemia is high in the general population and the increase of sd-LDL particles as well as large VLDL particles is a characteristic feature of familial combined hyperlipidemia, this assay would be quite useful for its diagnosis. Although sd-LDL is decreased by lipid-lowering drugs, such as statins and fibrates, the effect of adequate combination therapy on sd-LDL-C has not yet been confirmed; therefore, this assay would be also useful in determining the therapeutic strategy for patients with a high serum level of sd-LDL-C.

There are some limitations in our study. First, we

used plasma stored at −80℃, and there is no guarantee that we would have obtained the same results if we had used fresh serum; however, our results are consistent with those reported by Hirano *et al.*, who measured sd-LDL-C in a Japanese general population with the same method, and comparison studies performed in Japan indicate virtually identical results with the use of fresh vs. frozen plasma for sd-LDL-C[13]. Second, the single measurement of sd-LDL-C at the baseline survey and the fact we did not evaluate the longitudinal trend for each risk factor including lipid-lowering agents may have caused us to underestimate the relationship between these conditions and CAD due to regression dilution bias, although we statistically adjusted for the use of lipid-lowering agents at the baseline survey. Third, serum LDL-C was measured by the direct homogeneous assay, which failed to meet the National Cholesterol Education Program total error goals for diseased individuals, although it met these goals in non-diseased individuals[31]. However, the present study is a cohort study of community-dwelling citizens without a history of CVD. Furthermore, the serum levels of LDL-C determined by direct homogeneous assay are almost consistent with those calculated by the Friedewald formula in a large Japanese cohort.

Conclusions

In this large urban cohort study conducted in Japan, we demonstrated that sd-LDL-C is significantly associated with the development of CVD, providing evidence of sd-LDL-C as an important biomarker to predict CVD. A large intervention study is required to determine the appropriate target level of sd-LDL-C.

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Disclosures

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ORIGINAL ARTICLE
Ischemic Heart Disease

Effects of Voglibose and Nateglinide on Glycemic Status and Coronary Atherosclerosis in Early-Stage Diabetic Patients

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Background: Postprandial hyperglycemia and hyperinsulinemia have been considered as important determinants for the development of atherosclerosis. However, it remains to be elucidated whether correction of the postprandial glycemic status prevents atherosclerotic changes.

Methods and Results: The DIANA (DIAbetes and diffuse coronary NArrowing) study is a prospective randomized open-label multicenter trial. The 302 patients with coronary artery disease (CAD), impaired glucose tolerance/diabetes mellitus (DM) pattern according to 75-g oral glucose tolerance test and HbA_{1c} <6.9% were randomly assigned to life-style intervention (n=101), voglibose (0.9 mg/day, n=100) or nateglinide treatment (180 mg/day, n=101). We compared 1-year coronary atherosclerotic changes evaluated by quantitative coronary arteriography. Although voglibose significantly increased the number of patients with normal glucose tolerance at 1 year, there were no significant differences in coronary atherosclerotic changes at 1 year. However, overall, less atheroma progression was observed in patients in whom glycemic status was improved at 1 year (%change in total lesion length: 3.5% vs. 26.2%, P<0.01, %change in averaged lesion length: 0.7% vs. 18.6%, P=0.02).

Conclusions: Although coronary atherosclerotic changes were similar for voglibose and nateglinide, an improvement in glycemic status at 1 year was associated with less atheroma progression regardless of the treatment. Our findings underscore the management of glycemic abnormality to prevent coronary atherosclerotic changes in Japanese early-stage DM patients with CAD. (*Circ J* 2012; **76:** 712–720)

Key Words: Coronary artery atherosclerosis; Diabetes mellitus; Impaired glucose tolerance; Postprandial hyperglycemia

The prevalence of type 2 diabetes mellitus (DM) is increasing worldwide, and it is a major health problem associated with high cardiovascular morbidity and mortality.[1] Hyperglycemia is considered an important determinant for diabetic macrovascular disease,[2,3] and much attention has been focused on determining whether improving glycemic control leads to cardiovascular benefit. However, in patients with advanced DM, recent clinical trials have failed to demonstrate beneficial effects of intensive glycemic control on macrovascular disease.[4–6]

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In early-stage DM, impaired glucose tolerance (IGT), postprandial hyperglycemia (PPG) and insulin resistance/hyperinsulinemia play critical roles in the development of diabetic atherosclerosis.[7–11] We used quantitative coronary angiography (QCA) analysis to demonstrate that PPG is associated with the development of coronary atherosclerosis.[12] Although this observation emerges a concept that pharmacological therapies targeting glycemic abnormalities in early-stage DM may at-

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tenuate atheroma progression, this has yet to be demonstrated in an appropriately powered randomized clinical trial.

Voglibose is an inhibitor of carbohydrate absorption and reduces the postprandial glucose level without stimulating insulin secretion, whereas nateglinide improves PPG by insulin secretion. A clinical trial using these 2 drugs may enable investigation of the anti-atherosclerotic effect of these pharmacological interventions targeting PPG and the mechanisms linking abnormal glucose metabolism to cardiovascular disease. Therefore, we conducted the DIANA (DIAbetes and diffuse coronary NArrowing) study, which is the first study to compare the efficacy of voglibose, nateglinide and life-style interventions on the changes in coronary atherosclerosis in early-stage DM patients with coronary artery disease (CAD).

Methods

Design Overview

The DIANA study is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry (no. UMIN 0000107), and is a prospective randomized open-label, blinded assessment of endpoint trial conducted at 12 participating institutes in Japan. Approval to conduct the study was obtained from the ethics committee of each study center. The present study was an investigator-initiated trial that was designed, conducted, analyzed, and interpreted independently of sponsors. The membership of the writing committee and the management committee did not include any sponsor representatives. An independent data and safety monitoring committee whose members were unaware of study-group assignments monitored safety.

Participants

Patients were eligible if they had both CAD and IGT or newly diagnosed DM by 75-g oral glucose tolerance test (75 g-OGTT). The diagnosis of CAD was documented by coronary arteriography (CAG: ≥75% stenosis of a major epicardial coronary artery associated with a positive stress test for myocardial ischemia). IGT was defined as fasting plasma glucose (FPG) level <7.0 mmol/L and a postprandial glucose level (120-min post-load glucose level) ≥7.8 mmol/L but <11.1 mmol/L. Newly diagnosed DM was defined as FPG level ≥7.0 mmol/L and/or a postprandial glucose level ≥11.1 mmol/L. Because the Japan Diabetes Society defined diabetic patients with glycosylated hemoglobin (HbA_{1c}) ≥6.9% (National Glycohemoglobin Standardization Program: NGSP) as 'insufficiently-controlled hyperglycemia' when we started the patients' enrollment in 2005, we recruited early-stage diabetic patients with HbA_{1c} <6.9% (NGSP).[13] The following patients were excluded: acute myocardial infarction within 24 h of onset; history of coronary artery bypass surgery; previous treatment with any antidiabetic therapy; serum creatinine level ≥176.8 μmol/L. All participants provided written informed consent.

Randomization and Interventions

All eligible patients were encouraged to start a low-calorie diet and mild to moderate exercise. The goal of the life-style intervention was to achieve and maintain a weight reduction of at least 7% of initial body weight and to engage in moderate physical activity for at least 150 min per week.[14] Patients were then randomly assigned to life-style intervention only (diet and exercise therapy), 0.9 mg voglibose 3 times daily or 180 mg nateglinide 3 times daily. Randomization was performed via the internet using a computer program with a stratified allocation procedure designed to balance the 3 treatment groups with respect to glycemic status (IGT or DM). If hypoglycemia occurred in the pharmacological groups, the dose of drug was reduced or discontinued at the doctor's discretion. Although the use of other antidiabetic drugs was prohibited, cardiovascular medications were allowed at the doctor's discretion.

Follow-up Schedule

All patients were scheduled to attend monthly visits for the first 2 months and then additional visits were determined at each outpatient clinic doctors' discretion. At study visits, assessments were conducted for glycemic and metabolic profiles, as well as tolerability of the study treatments and occurrence of adverse events. Adverse effects of therapy were carefully audited to ensure the safety of the patients. At the 1-year final visit, all this information was collected, and follow-up CAG and 75 g-OGTT were performed.

Laboratory Measurements

Venous blood samples for the 75 g-OGTT were taken before and at 120 min after the glucose load. The World Health Organization criteria were used for classifying the OGTT results.[15] NGT was defined as FPG level <6.1 mmol/L and a postprandial glucose level <7.8 mmol/L. Impaired fasting glucose was defined as FPG level ≥6.1 mmol/L but <7.0 mmol/L and a postprandial glucose level <7.8 mmol/L.

HbA_{1c}, serum levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), creatinine levels, and levels of urinary albumin, adiponectin, high-molecular-weight adiponectin and high-sensitivity C-reactive protein (hs-CRP) were measured before and 1-year after the randomization. Considering the relational expression of HbA_{1c} (NGSP) and HbA_{1c} (Japan Diabetes Society) measured by the previous Japanese standard substance and measurement methods, the value for HbA_{1c} is estimated as an NGSP equivalent value calculated by the following formula: HbA_{1c} (NGSP) = HbA_{1c} (Japan Diabetes Society) + 0.4%.

Insulin sensitivity was assessed by 75 g-OGTT using the following formula:[16]

$$\text{Matsuda index} = 10{,}000/\sqrt{(\text{FPG} \times \text{fasting plasma insulin}) \times (\text{mean concentration of 75 g-OGTT plasma glucose levels} \times \text{mean concentration of 75 g-OGTT plasma insulin concentration})}$$

The hs-CRP level was assayed using a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Newark, DE, USA). Plasma adiponectin was assessed with adiponectin ELISA kits (Otsuka Pharmaceutical Co Ltd, Tokyo, Japan). High-molecular-weight adiponectin was assessed with high-molecular-weight adiponectin ELISA kits (Fujirebio Inc, Tokyo, Japan). Urinary albumin was measured by the Jaffe reaction. The spot urinary albumin (μg/ml)-to-creatinine (mg/ml) ratio was calculated for all participants.

CAG and QCA Analysis

CAG was performed in multiple projections after administration of intracoronary nitroglycerin (0.125–0.25 mg). As described previously, we calculated the averaged vessel diameter (AVD), total lesion length (TLL) and averaged lesion length (ALL) using QCA without including segments treated with percutaneous coronary intervention.[12,17] A computer-assisted quantitative analysis (CMS-QCA ver. 5.0, MEDIS, The Netherlands) was used to measure coronary atherosclerotic changes after each treatment. To accurately compare the 2 angiographic images at baseline and follow-up, the same angiographic

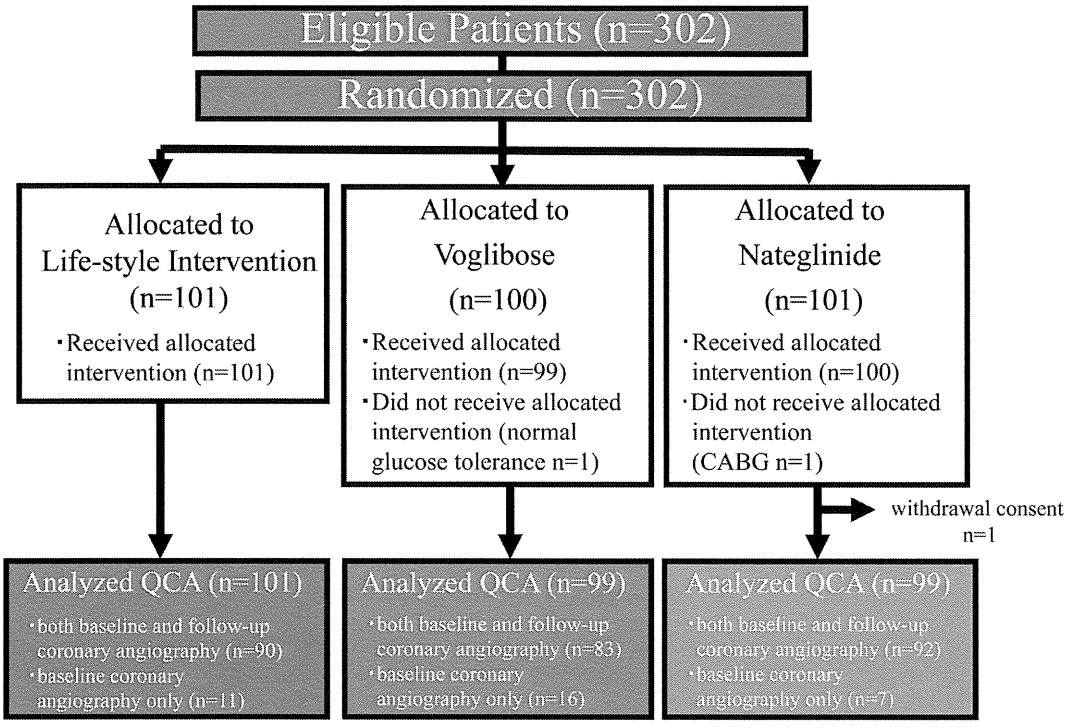

Figure 1. Trial profiles. CABG, coronary artery bypass grafting; QCA, quantitative coronary arteriography.

views of the left and right coronary arteries were obtained at each CAG session. The QCA data were assessed by 2 experienced cardiologists who were blinded to the glucose tolerance status and assigned group.

Primary and Secondary Outcomes

The primary endpoint was set as the change in TLL, ALL and AVD during follow-up. The secondary endpoint was set as changes in glycemic status and the occurrence of major adverse cardiovascular events (MACE: all-cause death, non-fatal myocardial infarction, coronary revascularization) at 1 year after randomization.

Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. QCA parameters at baseline were compared among the 3 groups by t-test, and the changes in QCA parameters were compared in each group by paired t-test. The primary efficacy parameters (changes in TLL, ALL and AVD) were analyzed using a general linear model, with treatment and glycemic status (IGT/DM) as a fixed effect. Changes in glycemic profile and metabolic parameters from baseline to 1 year were analyzed with t-tests. An improvement in glycemic status was defined as reversion of glycemic status from IGT to NGT, or from DM to IGT/NGT. As exploratory analysis, to estimate the underlying causal effects of an improvement in glycemic status, change in metabolic parameters, and medication use on atheroma progression, we used a marginal structural model with inverse probability weights.[18,19] The change in metabolic parameters from baseline to 1 year and the usage of drugs were dichotomized as increase/decrease and use/non-use, respectively. The probabilities of increase or use of these parameters were estimated by logistic regression containing baseline parameters: glycemic status (IGT or DM), sex, age, weight, body mass index, fasting and postprandial glucose and insulin levels, HbA_{1c}, HDL-C and LDL-C levels, log(hs-CRP), assigned treatment, and usage of statins, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. In the case of usage of a drug, the variable of the target drug was excluded from logistic regression. After estimating the probabilities of increase or use, the inverse of these probabilities were used as weights of the general linear model of TLL or ALL. Major adverse cardiovascular events were determined by log-rank test. The power ($1-\beta$) to detect 2 mm (SD=4 mm) in the pre-post difference of ALL between groups was >90 as statistical significance, given a total sample size of 300. Statistical significance was defined as a 2-sided P-value ≤0.05. The statistical analysis was done with SAS software (version 9.1, Cary, NC, USA).

Role of the Funding Source

This study was performed under the sponsorship of the Japan Cardiovascular Research Foundation. The organization had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Enrollment of Participants

Between February 1, 2005 and February 28, 2007, a total of 302 eligible patients were randomly assigned to life-style intervention (n=101), voglibose therapy (n=101) or nateglinide therapy (n=100), with follow-up ending on August 30, 2008 (Figure 1). Because of protocol violation, 2 patients did not receive an allocated intervention; 1 patient withdrew consent during this study period. Also, follow-up CAG was not per-

Table 1. Baseline Characteristics

	LI (n=101)	Voglibose (n=99)	Nateglinide (n=100)
Age (years)	65±9	65±10	64±10
Male, n (%)	88 (87)	85 (86)	86 (86)
DM, n (%)	43 (43)	42 (42)	43 (43)
IGT, n (%)	58 (57)	57 (58)	57 (57)
Diagnosis of CAD			
Angina pectoris, n (%)	38 (38)	41 (41)	26 (26)
Silent myocardial ischemia, n (%)	11 (11)	11 (11)	22 (22)
Previous myocardial infarction, n (%)	52 (51)	47 (47)	52 (52)

P=NS for all parameters.
LI, life-style intervention; DM, diabetes mellitus; IGT, impaired glucose tolerance; CAD, coronary artery disease.

Table 2. Glycemic Profile and Metabolic Parameters

	LI (n=101)		Voglibose (n=99)		Nateglinide (n=100)	
	Pre	1-year	Pre	1-year	Pre	1-year
Glycemic profile						
Fasting plasma glucose (mmol/L)	5.5±0.8	5.6±0.7	5.6±0.7	5.7±0.8	5.5±0.7	5.6±0.7
Postprandial glucose (mmol/L)	10.9±2.3	9.2±2.8#	10.9±2.6	8.8±3.2#,†	10.9±2.1	9.5±2.8#
Fasting plasma insulin (pmol/L)	49.8±57.0	45.0±32.4	48.0±38.4	43.2±36.0	46.8±29.4	46.8±27.6
Postprandial insulin (pmol/L)	600±342	462±306#	642±468	456±354#	720±528	576±432#
Matsuda index	5.5±3.1	7.7±6.0#	6.2±4.4	8.4±6.9#	5.3±3.2	6.2±4.2#
HbA_{1c} (%) [JDS]	5.6±0.4	5.6±0.4	5.5±0.4	5.5±0.4	5.5±0.4	5.4±0.4#
HbA_{1c} (%) [NGSP]	6.0±0.4	6.0±0.4	5.9±0.4	5.9±0.4	5.9±0.4	5.8±0.4#
Lipid profile						
Total cholesterol (mmol/L)	4.9±1.0	4.3±0.8#	4.9±0.9	4.5±0.7#	4.9±0.9	4.3±0.7#
Triglyceride (mmol/L)	1.8±1.0	1.9±1.4	1.6±1.1	1.6±1.2	1.8±1.1	1.6±0.9
HDL-C (mmol/L)	1.1±0.3	1.2±0.3#	1.1±0.3	1.2±0.3#	1.1±0.3	1.3±0.3#
LDL-C (mmol/L)	3.1±0.9	2.4±0.6#	3.2±0.9	2.7±0.6#	3.1±0.7	2.4±0.6#
LDL-C/HDL-C ratio	3.0±1.2	2.1±0.7#	3.1±1.0	2.3±0.7#	2.9±1.0	2.1±0.7#
Other parameters						
Adiponectin (mg/L)	7.8±4.2	8.9±5.1#	8.0±3.5	9.4±4.6#	7.5±3.8	8.7±3.7#
HMW adiponectin (mg/L)	3.9±3.4	4.7±3.2#	3.9±2.6	5.0±3.2#	3.6±2.2	4.5±2.8#
hs-CRP (mg/L)	6.1±12.4	2.6±9.3#	7.8±14.6	3.4±8.6#	7.4±20.2	1.5±3.4#
BUN (mmol/L)	5.4±1.4	6.1±1.8#	5.7±1.4	5.7±1.8	5.4±1.4	5.7±1.4#
Creatinine (μmol/L)	79.6±17.7	79.6±26.52	79.6±17.7	79.5±17.1	79.8±16.5	78.8±16.5
Urine albumin (mg/L)	36.4±175.5	17.6±35.8	16.6±24.3	64.1±401.7	15.8±41.9	20.5±55.6
Systolic blood pressure (mmHg)	123±16	127±15	123±14	127±17	125±16	126±16
Diastolic blood pressure (mmHg)	70±11	71±10	69±9	71±11	69±10	70±10
BMI (kg/m^2)	24.4±2.7	23.9±3.0#	24.6±3.5	24.3±3.2#	23.8±2.6	23.8±2.7
Medications						
β-blocker, n (%)	60 (59)	60 (59)	65 (66)	68 (69)	65 (65)	60 (60)
Calcium-channel blocker, n (%)	31 (31)	38 (38)	31 (31)	41 (41)	29 (29)	31 (31)
ACEI, n (%)	30 (30)	29 (29)	36 (36)	30 (30)	34 (34)	28 (28)
ARB, n (%)	33 (33)	42 (42)	27 (27)	33 (33)	34 (34)	45 (45)
Statins, n (%)	75 (74)*	86 (85)	55 (56)	75 (76)	64 (64)	71 (71)
Aspirin, n (%)	101 (100)	97 (96)	97 (98)	95 (96)	100 (100)	95 (95)
Thienopyridines, n (%)	82 (81)	48 (48)	83 (83)	38 (38)	74 (74)	41 (41)

#P<0.05 vs. pre; *P<0.05 vs. baseline value in the voglibose group; †P<0.05 vs. 1-year value in the nateglinide group.
HbA_{1c}, glycated hemoglobin; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization program; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HMW, high molecular weight; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Other abbreviation see in Table 1.

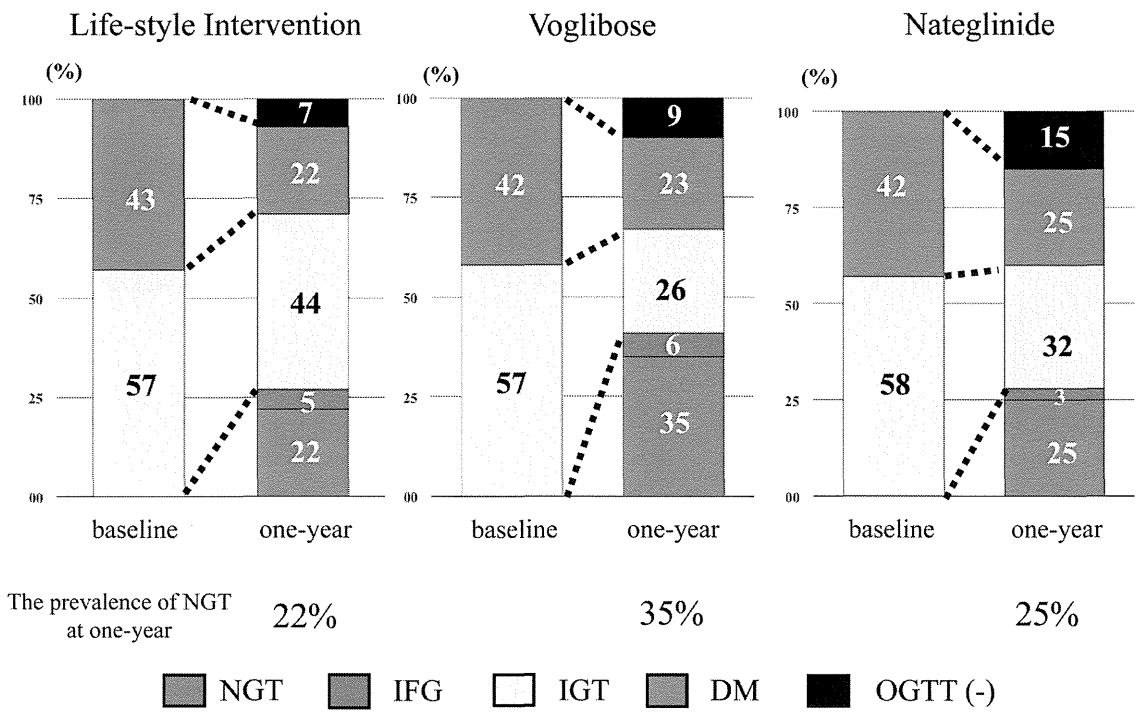

Figure 2. Comparison of the changes in glycemic status among the 3 treatment groups. DM, diabetes mellitus, IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Table 3. Changes in QCA Parameters

	LI	Voglibose	Nateglinide	P value	
				Voglibose vs. LI	Nateglinide vs. LI
Averaged vessel diameter (mm)					
n	90	83	92		
Baseline	2.81±0.35	2.84±0.37	2.83±0.37	0.56	0.66
1 year	2.78±0.34	2.80±0.35	2.80±0.39	0.55	0.60
Change at 1 year	−0.03±0.12	−0.04±0.11	−0.04±0.11		
P value compared with baseline	0.02	0.002	0.002		
Total lesion length (mm)					
n	90	83	92		
Baseline	10.09±11.19	10.38±10.83	11.69±13.52	0.86	0.39
1 year	10.53±11.02	11.14±10.26	11.78±14.12	0.59	0.55
Change at 1 year	0.45±3.56	0.77±3.95	0.09±4.40		
P value compared with baseline	0.24	0.08	0.84		
Averaged lesion length (mm)					
n	90	83	92		
Baseline	5.05±3.95	5.45±4.86	5.87±4.90	0.55	0.22
1 year	5.17±4.03	5.69±4.75	5.69±5.02	0.75	0.37
Change at 1 year	0.12±2.11	0.24±2.77	−0.18±2.32		
P value compared with baseline	0.59	0.43	0.47		

QCA, quantitative coronary angiography. Other abbreviation see in Table 1.

formed in 11, 16 and 7 patients in the life-style intervention, voglibose and nateglinide group, respectively. Therefore, follow-up QCA measurements were available in the remaining 265 patients. The baseline characteristics were well matched among the 3 groups (Table 1).

Glycemic and Other Metabolic Parameters Among the Treatment Groups

The baseline glycemic and metabolic parameters were also well matched (Table 2). In the voglibose group, 92% of patients received 0.9 mg and 5% of patients received 0.6 mg. In

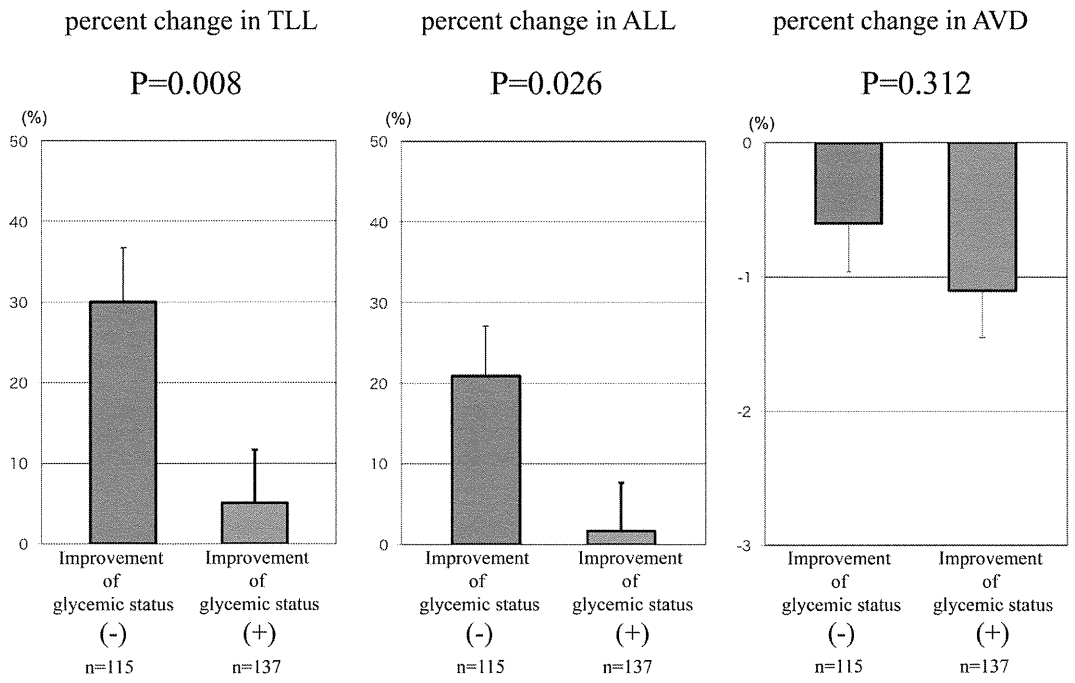

Figure 3. Comparison of percent change in each QCA parameter in patients with and without an improvement in glycemic status. *Improvement in glycemic status was defined as status changes from IGT to NGT, or from DM to NGT/IGT in a 1-year follow-up period. AVD, averaged vessel diameter; ALL, averaged lesion length; DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; QCA, quantitative coronary angiography; TLL, total lesion length.

Table 4. Effects of Various Metabolic Parameters on Change in TLL by Marginal Structural Model Analysis

	Estimated effects of change in TLL		
	β	95%CI	P value
Change in fasting glucose	−2.335	−3.784 to −0.886	0.002
Change in postprandial glucose	−0.035	−1.658 to 1.588	0.96
Change in fasting insulin	−6.347	−7.850 to −4.843	<0.001
Change in postprandial insulin	2.469	0.654 to 4.284	0.008
Change in HbA_{1c}	0.967	−0.258 to 2.190	0.12
Improvement in glycemic status (from DM to NGT/IGT, from IGT to NGT)	−6.190	−7.538 to −4.843	<0.001
Change in HDL-C	−3.648	−5.512 to −1.783	<0.001
Change in LDL-C	−5.711	−12.514 to 1.092	0.09
Change in log (hs-CRP)	0.023	−3.090 to 3.137	0.98
Usage of statins	1.593	0.186 to 3.000	0.02
Usage of ACEI	−0.095	−1.444 to 1.254	0.89
Usage of ARB	0.754	−0.514 to 2.022	0.24

TLL, total lesion length; NGT, normal glucose tolerance. Other abbreviations see in Tables 1,2.

the nateglinide group, 74% of patients received 180 mg and 22% of patients received 90 mg.

At follow-up, the voglibose group showed significantly lower postprandial glucose levels than the nateglinide group. Each treatment group showed favorable changes in other metabolic parameters, including body weight, body mass index, adiponectin, high-molecular-weight adiponectin and hs-CRP levels at follow-up, and these changes were similar across the 3 groups. Also, the lipid profile other than triglycerides was significantly improved and there were no significant differences in LDL-C levels or the LDL-C/HDL-C ratio at follow-up among the 3 groups. HbA_{1c} levels were significantly reduced in the nateglinide group.

In the present study, statins were more frequently used at baseline in the life-style intervention group than in the voglibose group (Table 2). However, there was no difference in the use of statins at follow-up. The use of other medications at baseline and follow-up was also similar among the 3 groups.

Changes in Glycemic Status

Figure 2 shows the change in glucose tolerance in each group. The incidence of reversion of glycemic status to NGT at 1 year

Table 5. Changes in QCA Parameters and Improvement in Glycemic Status

	LI	Voglibose	Nateglinide
% change in TLL (mean±SD)			
Improvement in glycemic status (–)	21.4±15.2	56.7±16.7	19.8±15.0
Improvement in glycemic status (+)	14.3±5.6	4.0±5.6	–3.7±5.9
P-value for patients with vs. without improvement in glycemic status	0.63	0.02	0.09
% change in ALL (mean±SD)			
Improvement in glycemic status (–)	18.5±14.1	33.1±15.5	18.3±13.9
Improvement in glycemic status (+)	9.0±5.2	2.3±5.2	–6.9±5.5
P-value for patients with vs. without improvement in glycemic status	0.52	0.12	0.08
% change in AVD (mean±SD)			
Improvement in glycemic status (–)	–0.5±0.7	–0.7±0.7	–0.4±0.6
Improvement in glycemic status (+)	–0.6±0.6	–0.9±0.6	–1.9±0.6
P-value for patients with vs. without improvement in glycemic status	0.92	0.92	0.09

ALL, averaged lesion length; AVD, averaged vessel diameter. Other abbreviations see in Tables 1,3,4.

was significantly higher in the voglibose group (35%) than in the life-style intervention (22%) and nateglinide (25%) groups (P<0.05). The percentage of patients who deteriorated from IGT to DM was comparable: 17%, 12% and 13% in the life-style intervention, voglibose and nateglinide groups, respectively.

Changes in Angiographic Parameters

The changes in QCA parameters are summarized in Table 3. Baseline TLL, ALL and AVD were comparable across the groups. Also, there were no significant differences among the groups in the changes in these QCA parameters at 1 year.

In the explanatory analysis, the relationship between the improvement in abnormal glucose tolerance and atheroma progression was analyzed in all patients except the 13 patients in whom 75 g-OGTT was not performed at 1 year. Of 252 patients, an improvement in glycemic status (from IGT to NGT, or from DM to IGT/NGT) occurred in 137 patients (54%), and these patients showed a reduction in the percent changes in TLL and ALL at 1 year (Figure 3). The improvement in glycemic status, change in HDL-C, fasting glucose, fasting and postprandial insulin levels, and statin use were significantly associated with the change in TLL (Table 4). These parameters also significantly correlated with the change in ALL. The percent changes in each QCA parameter among the 3 groups with and without an improvement in glycemic status are summarized in Table 5. In the voglibose group, disease progression reflected by the change in TLL was attenuated in patients with an improvement in glycemic status (P=0.02). Although favorable trends in the percent change in TLL/ALL, which lead to disease regression, were also observed in the nateglinide group with improved glycemic status, none of the comparisons achieved statistical significance (P=0.09 and 0.08, respectively).

Clinical Outcomes and Adverse Events

The occurrence of MACE was comparable among the 3 groups (life-style intervention vs. voglibose P=0.62, life-style intervention vs. nateglinide P=0.96), even when the analysis was limited to the hard endpoints of all-cause death and non-fatal myocardial infarction (Table S1).

Regarding drug-related adverse events, there were 8 hypoglycemia events (voglibose 4% vs. nateglinide 5%, P=0.85). Although the incidence of abdominal symptoms was significantly higher in the voglibose group (11% vs. 1%, P=0.04), the incidence of all adverse events was similar (18% vs. 10%, P=0.51).

Trial discontinuation because of an adverse event, including not only a definite but also a possible or probable relationship, occurred frequently in the voglibose group (13% vs. 3%, P=0.04). Trial discontinuation in the life-style intervention group was 4%.

Discussion

In the DIANA study, the effect of 2 pharmacological therapies on coronary atherosclerosis was comparable with that of life-style intervention, although voglibose significantly increased reversion to NGT at 1 year. Importantly, regardless of the type of treatment, an improvement in glycemic abnormality was associated with less progression of coronary atherosclerosis in early-stage DM patients with CAD.

Effect of Voglibose and Nateglinide on the Glycemic Profile

Voglibose improved PPG more favorably and resulted in a significant reversion of IGT/DM to NGT. Similar results were observed in previous clinical trials such as STOP-NIDDM (the Study TO Prevent Non-insulin-dependent diabetes mellitus) trial, Voglibose Ph-3 Study and NAVIGATOR (the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research).[20–22] In particular, Gao et al demonstrated that nateglinide treatment led to sustained postprandial hyperinsulinemia.[23] Given that hyperinsulinemia is a glycemic characteristic of most patients with IGT or early-stage DM,[9,10] the use of the short-acting secretagogue, nateglinide, for these patients may overstimulate pancreatic beta-cells, leading to subsequent cellular dysfunction and insufficient antiglycemic effect. Voglibose, which does not directly increase circulating insulin levels, seems rather to favorably improve the glycemic status than the short-acting secretagogue, nateglinide.[24]

Comparable Effect of Pharmacological and Life-Style Interventions on Coronary Atherosclerosis in Early-Stage DM Patients

In the present study, despite the more favorable efficacy of voglibose on glycemic status, any additional benefits of voglibose on coronary atherosclerosis beyond the other treatment groups were not observed. The relatively short follow-up period may make it difficult to detect the clinical effects of intervention targeting PPG. In the subanalysis of the STOP-NIDDM study, acarbose, an α-glucosidase inhibitor, slowed the progression of carotid intima-media thickening in IGT

patients during 3.9 years of follow-up.[25] Longer follow-up may clarify the efficacy of the current study's pharmacological interventions on coronary atherosclerosis. Because trial discontinuation for drug-related adverse events occurred more frequently in the voglibose group, discontinuation of this treatment may decrease the power of analysis or trade off the favorable effect of voglibose induced reversion to NGT.

It should be also noted that the life-style intervention group responded well to the non-pharmacological therapy, resulting in clinical benefits on various glycemic and metabolic parameters. Under these favorable changes, significant atheroma progression was not observed. These findings are comparable with result of the previous Lifestyle Heart trial showing that 1-year life-style intervention prevented, rather than caused regression of, coronary atherosclerosis in nondiabetic patients.[26] Considering that the life-style intervention controlled multifactorial risk factors with a low discontinuation rate, this intervention still seems to be an effective first-step therapeutic option for early-stage DM.

Therapeutic Significance of Glycemic Control for Atheroma Progression

To the best of our knowledge, the DIANA study is the first to demonstrate that an improvement in glycemic status is significantly associated with less atherosclerotic change. Given that PPG and hyperinsulinemia initiate a cascade of proatherogenic effects, including endothelial dysfunction, inflammation and oxidative stress,[27–30] our finding provides an important mechanistic link between glycemic abnormality and coronary atherosclerosis, especially in early-stage DM, and underscores glycemic management for the prevention of atheroma progression in this phase. There is a substantial body of studies using QCA that show a close relationship between angiographic atherosclerotic changes and the occurrence of future cardiovascular events.[31–33] Brown et al reported that atheroma progression, defined by 10% increase in diameter stenosis, predicts subsequent cardiovascular events.[31] Slowing the progression of coronary atherosclerosis, as shown in a reduction of changes in TLL/ALL, may prevent future cardiovascular events in early-stage DM patients with CAD. As shown in Table 5, achievement of an improved glycemic status by using anti-PPG drugs appears to provide greater benefit on the natural history of atheroma burden in Japanese early-stage DM patients with CAD. Because this subanalysis does not have adequate statistical power for analysis, due to the small sample size, further larger studies will be needed to confirm these results.

An increase in the HDL-C level also positively correlated with less atherosclerotic changes. HDL-C promotes reverse cholesterol transport and exerts favorable effects on inflammatory, oxidative and endothelial pathways.[34–37] These underlying mechanisms seem to have contributed to the favorable changes in the QCA parameters in our early-stage DM patients.

Because it is ethically difficult to have a control group in which life-style modification is prohibited, the present study was limited in its evaluation of the true efficacy of a drug intervention targeting PPG on coronary atherosclerosis.

Conclusions

In the DIANA study focused on Japanese early-stage DM patients with CAD, despite a higher incidence of reversion to NGT in the voglibose group, coronary atherosclerotic changes were similar among the 3 groups. However, regardless of the type of treatment, patients whose glycemic status improved showed attenuation of atheroma progression. These findings support the need for intensive management of glycemic abnormality in early-stage diabetes.

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Disclosures

The authors declare that they have no competing interests. Shunichi Miyazaki: Board membership of Daiichi-Sankyo Co and Johnson & Johnson Co. Also, payment for lectures, including service on speakers bureaus at MSD Co.

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