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Effect of Novel Stratified Lipid Risk by "LDL-Window" and Flow-Mediated Dilation on the Prognosis of Coronary Artery Disease Using the FMD-J Study A Data

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Background: Elevated levels of triglyceride (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) are regarded as a residual lipid risk in low-density lipoprotein cholesterol (LDL-C)-lowering therapy. This study investigated the association between lipid risk stratified by TG and non-HDL-C and the prognosis of patients with coronary artery disease (CAD), and the association between stratified lipid risk and flow-mediated dilatation (FMD) index.

Methods and Results: The 624 CAD patients enrolled in flow-mediated dilation (FMD)-J study A were divided into 4 groups: low-risk group (n=413) with TG <150 mg/dL and non-HDL-C <170 mg/dL; hyper-TG group (n=180) with TG ≥150 mg/dL and non-HDL-C <170 mg/dL; hyper-non-HDL group (n=12) with TG <150 mg/dL and non-HDL-C ≥170 mg/dL; and high-risk group (n=19) with TG ≥150 mg/dL and non-HDL-C ≥170 mg/dL. Comparison of the groups showed the cumulative incidence of a 3-point major adverse cardiovascular event (MACE) was different and highest in the high-risk group in all the patients (P=0.009), and in patients with a FMD index ≥7.0% (P=0.021), but not in those with a FMD index <7.0%. Multivariable regression analysis showed that high lipid risk (P=0.019) and FMD <7.0% (P=0.040) were independently correlated with the incidence of a 3-point MACE.

Conclusions: Novel stratification of lipid risk, simply using TG and non-HDL-C levels, combined with FMD measurement, is useful for predicting cardiovascular outcomes in patients with CAD.

Key Words: Coronary artery disease; Flow-mediated dilation; Lipid risk stratification; Non-high-density lipoprotein cholesterol; Triglyceride

High serum levels of small dense low-density lipoprotein (sd-LDL) are associated with the development of coronary artery disease (CAD).[1] Therefore, patients with a high sd-LDL level and even a low serum level of low-density lipoprotein cholesterol (LDL-C) may be at high risk of developing CAD compared to those with a low sd-LDL level. Nevertheless, the measurement of sd-LDL is uncommon in current clinical practice. A previous study demonstrated that an increase in serum triglyceride (TG) level minimized LDL particle size,[2] whereas an increase in serum non-high-density lipoprotein cholesterol (non-HDL-C) level correlated closely with the number of LDL particles.[3,4] Therefore, by stratifying the serum levels of TG and non-HDL-C, it may be

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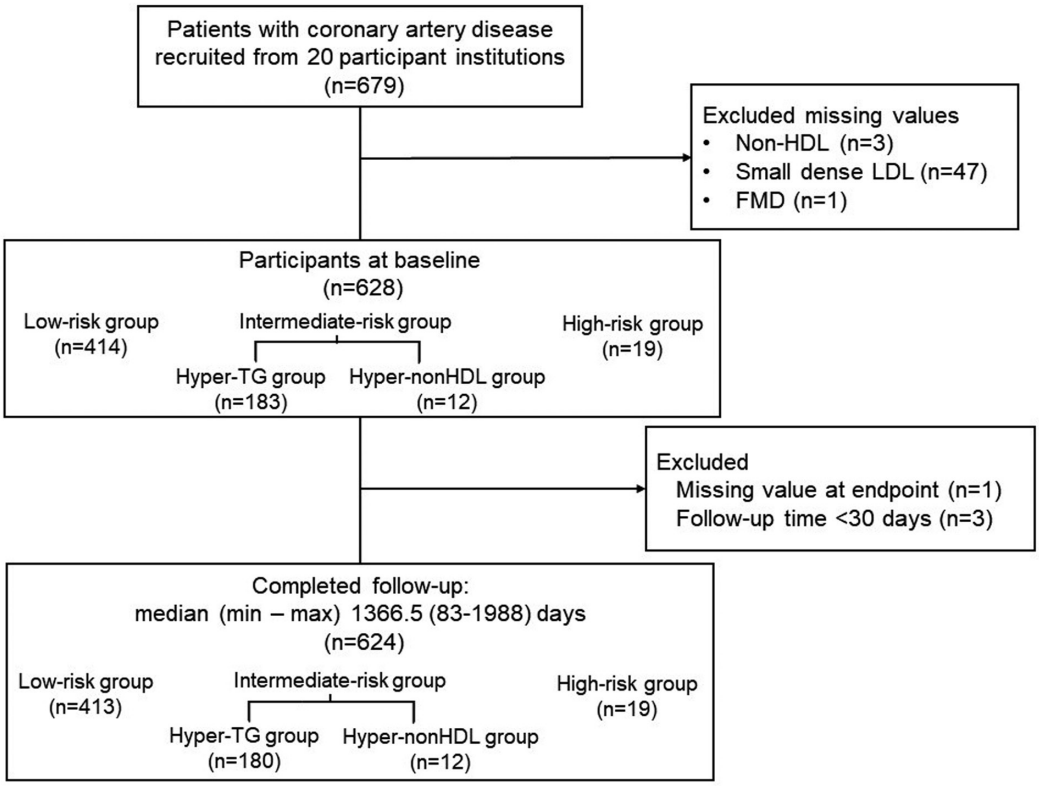

Figure 1. Flowchart of study patient selection and follow up. FMD, flow-mediated dilation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

possible to verify an increase in sd-LDL level, or in other words, hypertriglyceridemia and hyper-non-HDL-cholesterolemia may be regarded as residual risk for LDL-C lowering therapy. Hayashi et al[5] reported the impact of cut-off values based on 150 mg/dL for TG and 170 mg/dL for non-HDL-C, and introduced these cut-off values as an "alternative LDL window". In contrast, flow-mediated dilation (FMD) is used widely to assess endothelial function. The FMD-J study is a multicenter study that aimed to examine the usefulness and standardization of FMD assessment.[6] The study was designed to include 3 patient cohorts such as study A, B, and C. FMD-J study A assessed the impact of the FMD index on prognosis in patients with CAD. The present study, as a post-hoc analysis of FMD-J study A, investigated the association between lipid risk stratified by TG and non-HDL-C (i.e., LDL-window) and the prognosis of patients with CAD, and also the association between stratified lipid risk and the FMD index.

Methods

Study Population

The FMD-J Study A was a prospective, multicenter, observational, cohort study conducted at 22 university hospitals and affiliated clinics in Japan. A total of 679 patients aged 30–88 years diagnosed with CAD were enrolled in the study between May 1, 2010 and August 31, 2012. The protocol was registered at the University Hospital

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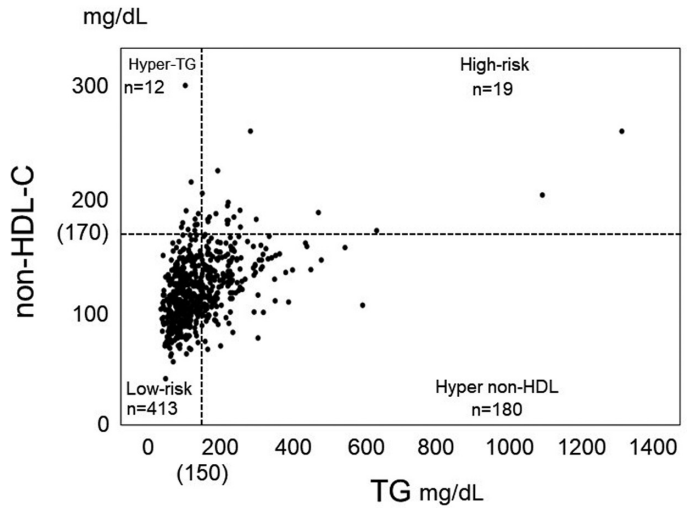

Figure 2. Distribution of TG and non-HDL-C levels and novel lipid risk stratification. Low-risk, TG <150 mg/dL and non-HDL <170 mg/dL (n=413); hyper-TG, TG ≥150 mg/dL and non-HDL <170 mg/dL (n=12); hyper-non-HDL group, TG <150 mg/dL and non-HDL ≥170 mg/dL (n=180); high-risk, TG ≥150 mg/dL and non-HDL ≥170 mg/dL (n=19). Non-HDL-C, non-high-density lipoprotein-cholesterol; TG, triglyceride.

Medical Information Network Clinical Trials Registry (UMIN000012950). Of the 679 enrolled patients, we excluded patients with missing main values (non-HDL; n=3, sd-LDL; n=47, FMD; n=1). The remaining 628 patients were followed up from baseline. The median follow-up period was 1,366 days (minimum 83 days, maximum 1,988 days). A total of 624 patients were followed up completely, with 1 patient with no record of endpoint and 3 with a follow-up period of <30 days excluded from the study (**Figure 1**).

Study Design

Based on cut-off values of 150 mg/dL for TG and 170 mg/dL for non-HDL-C,[5] we divided the patients into 4 lipid risk groups: the low-risk group (n=413) with TG <150 mg/dL and non-HDL-C <170 mg/dL; the hyper-TG group (n=180) with TG ≥150 mg/dL and non-HDL-C <170 mg/dL; the hyper-non-HDL group (n=12) with TG <150 mg/dL and non-HDL-C ≥170 mg/dL; and the high-risk group (n=19) with TG ≥150 mg/dL and non-HDL-C ≥170 mg/dL (**Figures 1** and **2**). The hyper-TG group and the hyper-non-HDL group were regarded as intermediate risk groups.

FMD was measured using high-resolution ultrasonography (UNEXEF18G; UNEX Co, Nagoya, Japan). The protocol for measurement of FMD has been described in detail elsewhere.[7] In the FMD-J study A, the cut-off value of the FMD index for predicting primary and secondary outcomes was defined as 7.1%.[8] Recently, the Japan Society for Vascular Failure proposed a cut-off value for the FMD index of 7.0% for normal to baseline and 4.0% for borderline to abnormal.[9] Therefore, in this study, we used 7.0% as the cut-off value for FMD.

A homogeneous assay method was used for the direct measurement of plasma levels of sd-LDL (sd-LDL-EX "Seiken"; Denka Seiken, Tokyo, Japan), carried out using a Hitachi 917 automated chemistry analyzer (Hitachi High-Tech Corporation, Tokyo, Japan).[10] The sd-LDL levels measured were divided into tertiles as follows: <24.4 mg/dL, ≥24.4 mg/dL, <36.4 mg/dL, and ≥36.4 mg/dL. We compared the incidence in the 4 lipid risk groups of a 3-point major adverse cardiovascular event (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (MI) and non-fatal stroke. A composite of non-fatal MI and non-fatal stroke was also compared. A detailed explanation of the registry design and establishment of the FMD-J study has been published previously.[5] The study protocol conformed to the principles of the Declaration of Helsinki (1964) and the study was conducted with the approval of the ethical guidelines committee of each of the participating institutions.

Statistical Analysis

Comparison of the CAD patients in the 4 lipid risk groups and the 2 FMD groups was carried out using the Chi-squared test for categorical variables and analysis of variance or the Kruskal-Wallis test for continuous variables in 3 groups, and the Mann-Whitney U-test or the Student's t-test for continuous variables in 2 groups. Individual missing values were annotated in each table and analysis. Univariate and multivariate Cox proportional hazards regression analyses were performed to analyze clinical outcomes stratified according to lipid risk and cut-off value of FMD. The trend test was used to examine the dose-response relationship of clinical outcomes in the 4 lipid risk groups. Kaplan-Meier survival analysis was performed to analyze the 3-point MACE in the 4 lipid risk groups for patients overall and for groups stratified according to the FMD. Each pair comparison was used in the log rank test. Person-years was calculated as 365 days of each follow-up days. Censored cases were defined by the occurrence of outcomes or drop-out from follow up. Two-tailed P values <0.05 were considered statistically significant. IBM SPSS Statistics 27.0 (IBM SPSS, Tokyo, Japan) was used for the statistical analyses.

Results

Comparison of the 4 Lipid Risk Groups

A comparison of the clinical background of the 4 lipid risk group patients is shown in **Table 1**. The age of the patients was significantly higher in the hyper-non-HDL group (P<0.001). Body mass index (P=0.001), TG (P<0.001), sd-LDL (P<0.001), and malondialdehyde-modified LDL (MDA-LDL) (P<0.001) were highest in the high-risk group. The serum level of total cholesterol (TC) (P<0.001),

Table 1. Comparison of Clinical Patient Backgrounds on the Basis of Lipid Risk Stratification

	Total (n=624)	Low-risk (n=413)	Hyper-TG (n=180)	Hyper-non-HDL (n=12)	High-risk (n=19)	P value*
Demographics						
Female gender	96 (15.4)	73 (17.7)	19 (10.6)	0 (0.0)	4 (21.1)	0.057
Age, years	64.1±8.3	64.9±8.1	62.1±8.6	67.4±7.7	61.6±8.3	<0.001
Lifestyle						
Current smoker	85 (14.0)	51 (12.7)	30 (17.3)	3 (25.0)	1 (5.6)	0.215
Alcohol intake	263 (43.3)	169 (41.8)	79 (45.7)	6 (50.0)	9 (50.0)	0.730
Exercise	355 (59.3)	241 (60.6)	95 (55.6)	7 (58.3)	12 (66.7)	0.646
Clinical parameters						
BMI, kg/m^2	24.8±3.6	24.5±3.6	25.4±3.5	24.7±2.9	27.1±4.0	0.001
SBP, mmHg	129.0±16.8	129.01±17.1	128.4±16.1	135.9±18.6	129.2±14.8	0.521
DBP, mmHg	74.5±10.7	74.1±10.9	74.8±10.5	77.1±10.5	78.1±10.1	0.327
Heart rate, beats/min	66.7±11.8	66.6±11.7	67.6±12.4	59.1±8.2	65.1±9.5	0.095
TC, mg/dL	170.6±30.9	163.5±26.1	174.6±24.3	245.2±35.3	240.3±24.2	<0.001
HDL-C, mg/dL	50.5±13.4	53.0±13.5	45.2±11.5	50.8±16.7	45.4±9.9	<0.001
Non-HDL-C, mg/dL	120.1±29.9	110.8±23.1	129.4±21.7	194.4±35.9	194.9±25.8	<0.001
TG, mg/dL	139.7±100.3	93.9±27.9	223.2±76.2	118.9±18.2	358.9±321.3	<0.001**
LDL-C, mg/dL	93.1±26.7	91.7±22.3	86.1±22.2	170.6±36.7	148.0±21.5	<0.001
sd-LDL, mg/dL	33.3±14.9	27.0±9.9	43.6±13.7	44.8±15.9	62.9±20.0	<0.001
MDA-LDL, U/L	115.1±38.8	108.1±36.1	124.1±38.6	150.3±34.6	159.4±42.0	<0.001
Blood sugar, mg/dL	116.9±35.0	113.7±29.4	123.1±44.1	177.7±21.8	128.7±46.2	0.009
Uric acid, mg/dL	5.9±1.3	5.7±1.3	6.1±1.2	6.1±1.1	6.6±1.3	<0.001
Framingham risk score, point	12.5±7.6	11.3±6.9	14.1±7.4	24.2±11.5	16.7±9.8	<0.001**
FMD, %	4.7±2.8	4.6±2.7	4.9±3.1	5.0±2.2	4.9±1.9	0.436**
FMD ≥7%	109 (17.5)	63 (15.3)	43 (23.9)	1 (8.3)	2 (10.5)	0.049
Metabolic syndrome	259 (41.5)	154 (37.3)	88 (48.9)	4 (33.3)	13 (68.4)	0.004
Concomitance						
Hypertension	585 (93.8)	385 (93.2)	171 (95.0)	12 (100.0)	17 (89.5)	0.558
Medication for hypertension	575 (92.1)	379 (91.8)	167 (93.8)	12 (100.0)	17 (89.5)	0.708
Dyslipidemia	582 (93.3)	373 (90.3)	180 (100.0)	10 (83.3)	19 (100)	<0.001
Medication for dyslipidemia	554 (88.8)	365 (88.4)	163 (90.6)	12 (100.0)	14 (73.7)	0.090
Diabetes mellitus	230 (36.9)	151 (36.6)	73 (40.0)	1 (8.3)	5 (26.3)	0.103
Medication for diabetes mellitus	189 (30.3)	129 (31.2)	56 (31.1)	1 (8.3)	3 (15.8)	0.182

Data are presented as n (%) or mean±standard deviation. Low-risk, non-HDL-C <170 mg/dL and TG <150 mg/dL; hyper-TG, non-HDL-C <170 mg/dL and TG ≥150 mg/dL; hyper-non-HDL, non-HDL-C ≥170 mg/dL and TG <150 mg/dL; High-risk, non-HDL-C ≥170 mg/dL and TG ≥150 mg/dL. BMI, body mass index; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified LDL; non-HDL-C, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure; sd-LDL, small dense LDL; TC, total cholesterol; TG, triglyceride. Missing values (smoker=18, alcohol intake=17, exercise=25, and Framingham score=46) were excluded. *Four lipid risk groups were compared using the Chi-squared test or analysis of variance. **TG and FMD were compared by using the Kruskal-Wallis test.

HDL-C (P<0.001), LDL-C (P<0.001), blood sugar (P=0.009), and Framingham risk score (P<0.001) were highest in the hyper-non-HDL group. The percentage of patients with FMD ≥7.0% was highest in the hyper-TG group (P=0.049).

In the 4 lipid groups, the incidence of 3-point MACE was highest in the high-risk group (low-risk group, 12.1%; hyper-TG group, 17.8%; hyper-non-HDL group, 25.0%; high-risk group, 26.3%; P=0.051). High-risk stratification using the "LDL window" significantly predicted 3-point MACE (high-risk group vs. low-risk group: adjusted hazard ratio [HR], 5.690; 95% confidence interval [CI], 1.596–20.283; P=0.029). The adjusted HR was calculated using age, sex, BMI, systolic blood pressure, heart rate, sd-LDL, MDA-LDL, LDL-C, fasting blood sugar (FBS), uric acid, FMD, medication for hypertension, dyslipidemia and diabetes mellitus, smoking, alcohol intake, and exercise habits (**Table 2**).

It is well established that the presence of the metabolic syndrome (MetS) is an independent predictor for CAD;[11] therefore, we need to evaluate the prevalence of the MetS as a confounding factor, due to BMI in the high-risk group being significantly higher than in the other groups. However, abdominal circumference was not always measured during the study. We therefore defined MetS as obesity (BMI ≥25 kg/m^2), plus ≥2 of the following 3 criteria: FBS ≥110 mg/dL or taking antidiabetic medicine; TG ≥150 mg/dL or HDL-C <40 mg/dL or taking lipid-lowering medicine; and SBP ≥130 mmHg or DBP ≥85 mmHg or taking antihypertensive drugs.[12] The percentage of MetS (P=0.004) was highest in the high-risk group (**Table 1**). In patients with MetS, no difference in the incidence of 3-point MACE was observed between the groups; however, in patients without MetS, the incidence of 3-point MACE was highest in the high lipid-risk group (low-risk group, 12.0%; hyper-TG

Table 2. Comparison of Clinical Outcomes on the Basis of Lipid Risk Stratification

	Low-risk	Hyper-TG	Hyper-non-HDL	High-risk	P value
Total, n	413	180	12	19	
3-point MACE, n (%)	50 (12.1)	32 (17.8)	3 (25.0)	5 (26.3)	0.051*
Person-years	1,485	653	45	56	
Incidence of 3-point MACE, per 100 person-years	3.4	4.9	6.7	8.9	
Crude HR	Ref.	1.450	1.930	2.636	0.010****
95% CI		0931–2.261	0.601–6.195	1.051–6.613	
P value**		0.101	0.269	0.039	
Adjusted HR	Ref.	1.156	2.384	5.690	0.029****
95% CI		0.621–2.150	0.580–9.802	1.596–20.283	
P value***		0.647	0.228	0.007	
Metabolic syndrome, yes, n	154	88	4	13	
3-point MACE, n (%)	19 (12.3)	14 (15.9)	0 (0)	2 (15.4)	0.734*
Person-years	552	328	17	45	
Incidence of 3-point MACE, per 100 person-years	3.4	4.3	0.0	4.4	
Crude HR	Ref.	1.213	n/a	1.251	0.784****
95% CI		0.607–2.422		0.291–5.378	
P value**		0.585		0.763	
Adjusted HR	Ref.	1.269	n/a	3.610	0.500****
95% CI		0.490–3.286		0.291–44.733	
P value***		0.623		0.317	
Metabolic syndrome, no, n	259	92	8	6	
3-point MACE, n (%)	31 (12.0)	18 (19.6)	3 (37.5)	3 (50.0)	0.007*
Person-years	933	325	28	11	
Incidence of 3-point MACE, per 100 person-years	3.3	5.5	10.6	26.8	
Crude HR	Ref.	1.678	3.193	8.738	<0.001****
95% CI		0.938–2.999	0.957–10.460	2.636–28.964	
P value**		0.081	0.055	<0.001	
Adjusted HR	Ref.	1.375	2.525	12.664	0.013****
95% CI		0.548–3.453	0.558–11.419	2.435–65.856	
P value***		0.498	0.229	0.003	

Low-risk, non-HDL-C <170 mg/dL and TG <150 mg/dL; hyper-TG, non-HDL-C <170 mg/dL and TG ≥150 mg/dL; hyper-non-HDL, non-HDL-C ≥170 mg/dL and TG <150 mg/dL; high-risk, non-HDL-C ≥170 mg/dL and TG ≥150 mg/dL. CI, confidence interval; HR, hazard ratio; MACE, major cardiovascular event; Ref., reference. Other abbreviations as in Table 1. *Using the Fisher's exact test. **Using the univariate Cox proportional hazard analysis. ***Using the multivariable Cox proportional hazard model adjusted for age, sex, BMI, SBP, sd-LDL, MAD-LDL, LDL-C, blood sugar, uric acid, FMD, medication for hypertension, dyslipidemias and diabetes mellitus, smoking, alcohol intake, and exercise habits. ****Using the trend test. The "metabolic syndrome" was defined as obesity (BMI ≥25 kg/m^2), plus ≥2 of the following 3 criteria: FBS ≥110 mg/dL or taking diabetes medication; TG ≥150 mg/dL or HDL-C <40 mg/dL or taking lipid-lowering medication; SBP ≥130 mmHg or DBP ≥85 mmHg or taking hypertension drugs.

group, 19.6%; hyper-non-HDL group, 37.5%; high-risk group, 50.0%; P=0.007). As shown in **Table 2**, this high-risk stratification significantly predicted 3-point MACE (high-risk group vs. low-risk group: adjusted HR, 12.664; 95% CI, 2.435–65.856; P=0.013).

The incidence of composite non-fatal MI and non-fatal stroke was highest in the high-risk group (low-risk group, 10.9%; hyper-TG group, 16.7%; hyper-non-HDL group, 25.0%; high-risk group, 26.3%; P=0.045). There was no difference in the incidence of the composite non-fetal MI and non-fetal stroke in patients with MetS. In contrast, in patients without MetS, the composite was highest in the high-risk group (low-risk group, 11.2%; hyper-TG group, 18.5%; hyper-non-HDL group, 37.5%; high-risk group, 50.0%; P=0.004) (**Supplementary Table 1**). No difference in the incidence of cardiovascular death was observed between the lipid risk groups (low-risk group, 1.7%; hyper-TG group, 1.1%; hyper-non-HDL group, 0.0%; high-risk group, 0.0%; P=0.855) (**Supplementary Table 2**).

Comparisons Based on the Cut-Off Value of FMD

The study subjects were divided into 2 groups based on a cut-off value of FMD of 7.0%. The comparison of the clinical background between the 2 FMD groups is shown in **Table 3**. Patients with a FMD <7.0% were older than those with a FMD ≥7.0% (P=0.004); otherwise, there were no significant differences in the clinical characteristics between the 2 groups.

The incidence of 3-point MACE was higher in patients with a FMD <7.0% than in those with a FMD ≥7.0% (15.7% vs. 8.3%; P=0.044). FMD <7.0% significantly predicted 3-point MACE (adjusted HR, 2.073; 95% CI, 1.029–4.176; P=0.041). The incidence of the composite of non-fatal MI and non-fatal stroke was significantly higher in patients

Table 3. Comparison of Patient Characteristics on the Basis of the Cut-Off Value for FMD

	FMD ≥7.0% (n=109)	FMD <7.0% (n=515)	P value
Demographics			
Female gender	19 (17.4)	77 (15.0)	0.514
Age, years	62±8.6	64.5±8.2	0.004
Lifestyle			
Current smoker	13 (12.0)	72 (14.5)	0.511
Alcohol intake	48 (44.0)	215 (41.7)	0.796
Exercise	56 (53.8)	299 (60.4)	0.216
Clinical parameters			
BMI, kg/m^2	24.6±3.6	24.9±3.6	0.412
SBP, mmHg	128.4±18.2	129.1±16.5	0.709
DBP, mmHg	75.0±11.7	74.4±10.5	0.578
Heart rate, beats/min	68.2±12.6	66.3±11.6	0.128
TC, mg/dL	171.3±27.7	170.4±31.5	0.789
HDL-C, mg/dL	50.0±12.0	50.6±13.7	0.720
Non-HDL-C, mg/dL	121.3±30.0	119.9±30.5	0.663
TG, mg/dL	148.1±83.0	137.9±103.5	0.084
LDL-C, mg/dL	91.8±25.5	92.8±27.3	0.725
sd-LDL, mg/dL	34.1±15.3	33.1±14.8	0.512
MDA-LDL, U/L	117.1±39.6	114.6±38.6	0.548
Blood sugar, mg/dL	112.4±296	117.9±36.0	0.138
Uric acid, mg/dL	5.9±1.1	5.8±1.3	0.595
Framingham risk score, point	11±6.8	12.8±7.7	0.022
Metabolic syndrome	43 (39.4)	216 (41.9)	0.631
Concomitance			
Hypertension	102 (93.6)	483 (93.8)	0.935
Medication for hypertension	99 (90.8)	476 (92.4)	0.572
Dyslipidemia	106 (97.2)	476 (92.4)	0.068
Medication for dyslipidemia	101 (92.7)	453 (88.0)	0.158
Diabetes mellitus	36 (33.0)	194 (37.7)	0.361
Medication for diabetes mellitus	28 (25.7)	161 (31.3)	0.250

Data are presented as n (%) or mean±standard deviation. Abbreviations as in Table 1. The FMD ≥7.0% and FMD <7.0 groups were compared using the Chi-squared test or Student's t-test. TG was compared using the Mann-Whitney U-test.

with a FMD index <7.0% than in those with a FMD index ≥7.0% (14.6% vs. 7.3%; P=0.044). A FMD index <7.0% significantly predicted the composite events (adjusted HR, 2.265; 95% CI, 1.074–4.779; P=0.032). There was no significant difference in the incidence of cardiovascular death between the 2 groups (0.9% vs. 1.6% in patients with a FMD index ≥7.0% or <7.0%, respectively; P=0.937; **Table 4**).

Association Between Clinical Outcome and Lipid Risk Stratification Combined With FMD

Figure 3 shows a comparison of the Kaplan-Meier survival curves for 3-point MACE in the 4 lipid risk groups, displayed separately as patients overall, patients with a FMD index ≥7.0%, and those with FMD <7.0%. In the patients overall, significant differences were observed in the cumulative event-free survival rate between the 4 lipid risk groups (comparison of the 4 groups, P=0.009; high-risk vs. low-risk, P=0.034; high-risk vs. hyper-TG, P=0.021; high-risk vs. hyper-non-HDL, P=0.729). In patients with a FMD index ≥7.0%, there were also significant differences between the 4 lipid risk groups (comparison of the 4 groups, P=0.021; high-risk vs. low-risk, P<0.001; high-risk vs. hyper-TG, P=0.027; high-risk vs. hyper-non-HDL, P=0.480). In patients with a FMD index <7.0%, no significant differences were observed between the 4 lipid risk groups (comparison of the 4 groups, P=0.037; hyper-TG vs. low-risk, P=0.172; high-risk vs. low-risk, P=0.553; hyper-TG vs. hyper-non-HDL, P=0.990; **Figure 3**).

Univariate and Multivariate Cox Regression Analysis for 3-Point MACE

Univariate regression analysis showed that the incidence of 3-point MACE correlated significantly with exercise habits (HR, 0.621; 95% CI, 0.409–0.944, P=0.026), systolic blood pressure (HR, 1.015; 95% CI, 1.003–1.027, P=0.017), blood sugar (HR, 1.005; 95% CI, 1.001–1.009, P=0.019), high-risk vs. low-risk (HR, 2.636; 95% CI, 1.051–6.613, P=0.039), FMD <7.0% vs. ≥7.0% (HR, 2.024; 95% CI 1.016–4.029, P=0.045), sd-LDL ≥36.4 vs. <24.4 mg/dL (HR, 1.859; 95% CI, 1.094–3.160, P=0.021) and medication for dyslipidemia (HR, 3.945; 95% CI, 1.248–12.473, P=0.019). Multivariable regression analysis showed that the incidence of 3-point MACE was significantly correlated with high-risk vs. low-risk (adjusted HR, 3.560; 95% CI, 1.230–10.306, P=0.019), FMD <7.0% vs. ≥7.0% (adjusted HR, 2.096; 95% CI, 1.034–4.251, P=0.040) and

Table 4. Comparison of Clinical Outcomes on the Basis of Cut-Off Value of FMD

	FMD ≥7% (n=109)	FMD <7% (n=515)	P value
3-point MACE	9 (8.3)	81 (15.7)	0.044*
Person-years	412	1,827	
Incidence of 3-point MACE, per 100 person-years	2.2	4.4	
Crude HR	Ref.	2.204	0.045**
95% CI		1.016–4.029	
Adjusted HR	Ref.	2.097	0.040***
95% CI		1.034–4.251	
Non-fatal MI and stroke	8 (7.3)	75 (14.6)	0.044*
Person-years	412	1,823	
Incidence of non-fatal MI and stroke, per 100 person-years	2.2	4.3	
Crude HR	Ref.	2.108	0.045**
95% CI		1.017–4.370	
Adjusted HR	Ref.	2.265	0.032***
95% CI		1.074–4.779	
Cardiovascular death	1 (0.9)	8 (1.6)	0.515*
Person-years	423	1,974	
CV mortality, per 100 person-years	0.2	0.4	
Crude HR	Ref.	1.707	0.614**
95% CI		0.214–13.651	
Adjusted HR	Ref.	1.940	0.596***
95% CI		0.167–22.474	

Data are presented as n (%) unless otherwise stated. MI, myocardial infarction. Other abbreviations as in Tables 1,2. *Using the Fisher's exact test. **Using univariate Cox proportional hazard analysis. ***Using the multivariable Cox proportional hazard model after adjustment for age, sex, BMI, SBP, HDL-C, TG, sd-LDL-C, MDA-LDL, blood sugar, uric acid, medication for hypertension, dyslipidemias and diabetes mellitus, smoking, alcohol intake, and exercise habits, but excluding missing values (smoker=18, alcohol intake=17, exercise=25, and uric acid=1).

medication for dyslipidemia (adjusted HR, 4.219; 95% CI, 1.312–13.570, P=0.016). The adjusted HR was calculated using age, sex, smoking, alcohol intake, exercise habit, body mass index, systolic blood pressure, heart rate, sd-LDL, MDA-LDL, blood sugar, uric acid, FMD, and medication for hypertension, dyslipidemia, and diabetes mellitus. Missing values (smoker=18, alcohol intake=17, exercise=25, LDL-C=10, and uric acid=1) were excluded from the univariate or multivariable analyses. Diastolic BP, TC, TG, LDL-C, and HDL-C were not entered into the multivariate analysis in order to avoid multicollinearity (**Table 5**).

Discussion

In this sub-analysis of the FMD-J study A, we proposed a novel lipid risk stratification, simply using TG and non-HDL-C levels. Setting the cut-off values for TG and non-HDL-C to 150 mg/dL and 170 mg/dL, respectively, we divided patients into 4 lipid risk groups. As a consequence, a major finding of this study was that the incidence of 3-point MACE increased with increasing stratified lipid risk in the entire study cohort. Interestingly, this association was evident in patients with a normal FMD index (≥7.0%), but absent in those with a low FMD index (<7.0%). This result suggests a rationale for lipid risk stratification as a predictor of cardiovascular outcomes in patients with CAD.

The increase in non-HDL-C is primarily influenced by the increase in LDL-C or remnant cholesterol level. Moreover, not only an increase in sd-LDL, but also an increase in remnant cholesterol, affects the atherogenicity in patients with hyper-non-HDL-cholesterolemia. The elevated LDL-C level is an exacerbation factor for vascular endothelial function. According to the Japan Atherosclerosis Society guidelines in 2017,[13] the mean values of LDL-C and non-HDL-C of our cohort indicated that the lipid management target for patients with CAD had not been achieved. "LDL-C <70 mg/dL" is presently the accepted target value for the secondary prevention for CAD worldwide; however, for HDL-C, TG, and non-HDL-C, no definite conclusion has been derived regarding their accurate target values for secondary prevention. In the Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD) trial conducted in Japan, the median value of LDL-C of <70 mg/dL was not achieved despite high-intensity statin usage.[14] Indeed, treatment with only statin is not very effective; therefore, non-statin LDL-C-lowering agents, such as ezetimibe[15] or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, may need to be administered.[16,17] Nevertheless, cardiovascular events may occur even under treatment with PCSK9 inhibitors.[18] It is therefore necessary to look at residual risk for CAD beyond LDL-C levels. In this regard, hypertriglyceridemia and hypo-HDL-cholesterolemia have attracted increasing attention as components of residual risk. However, appropriate treatment for increasing the HDL-C level has not yet been found and therefore the current target may be TG lowering and desired value setting in TG. There is evidence that omega-3

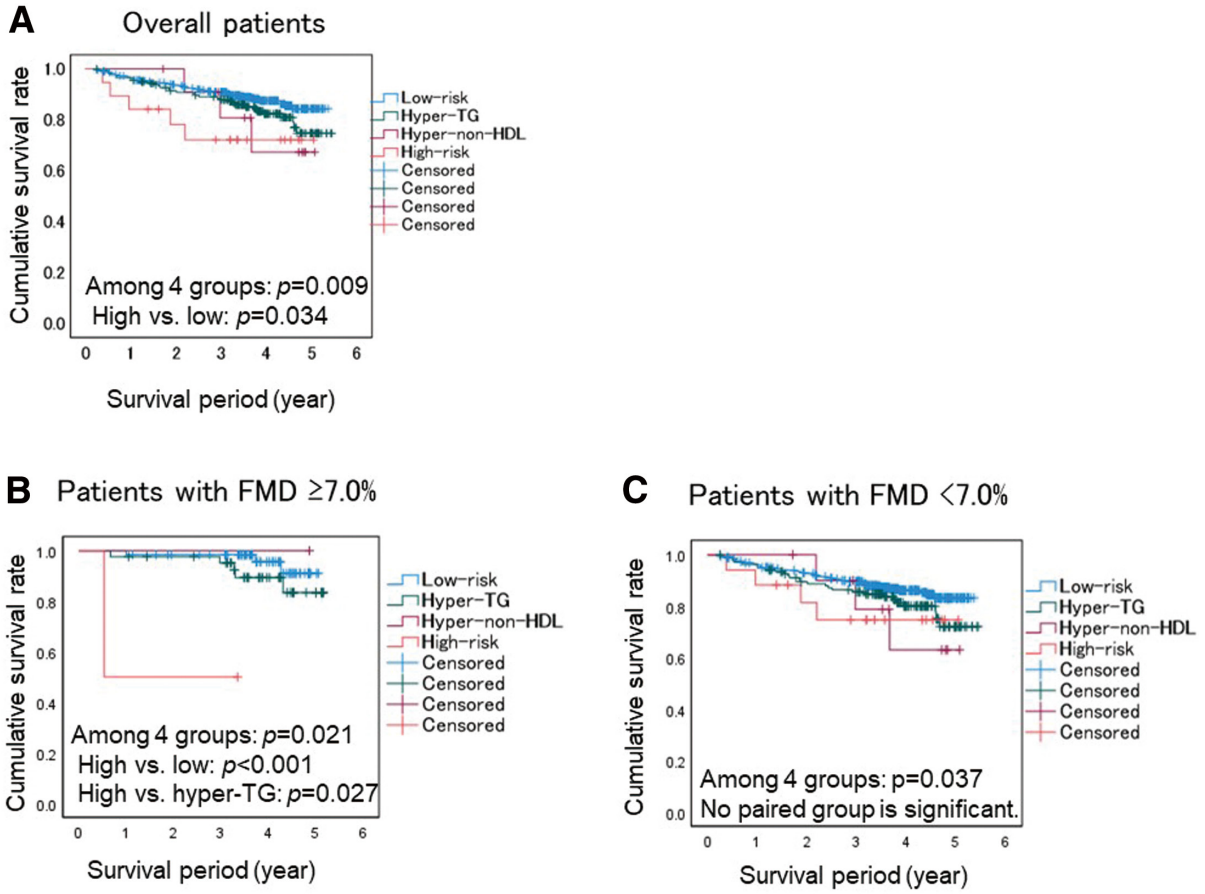

Figure 3. Association between survival rate of 3-point MACE and FMD. Kaplan-Meier curves for a 3-point MACE, defined as a composite of cardiac death, non-fatal MI and non-fatal stroke, compared between the 4 lipid risk groups for patients overall (**A**), patients with a FMD value ≥7.0% (**B**), and those with a FMD value <7.0% (**C**). FMD, flow-mediated dilation; MACE, major adverse cardiovascular event; MI, myocardial infarction.

polyunsaturated fatty acid intake decreases serum TG level,[19] whereas a selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-α), pemafibrate, is regarded as a promising agent for targeting TG levels.[20] Matsumoto et al reported that the stratification based upon an eicosapentaenoic acid/arachidonic acid ratio of 0.4 and a TG level of 150 mg/dL may be useful in predicting the occurrence of MACE after percutaneous coronary intervention.[21] Post-hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE-IT TIMI) 22 trial showed that a TG level <150 mg/dL was associated with a lower risk of recurrent cardiovascular events in patients with acute coronary syndrome, independent of the effect of LDL-C lowering.[22] As mentioned above, TG levels are associated with LDL particle size and non-HDL-C with LDL-particle number. A previous study demonstrated that even if serum LDL-C levels were decreased to <100 mg/dL, high sd-LDL levels impaired cardiovascular outcomes.[1] The "alternative LDL window", stratified by non-HDL-C and TG levels, showed a relationship with sd-LDL levels in healthy subjects and patients with either diabetes or CAD.[5] To the best of our knowledge, the present sub-analysis is the first to demonstrate an association between this novel lipid-risk stratification and long-term outcomes of patients with CAD. Our study also demonstrated an association between this stratification and endothelial function estimated by FMD.

The present study showed that the "alternative LDL window" was a powerful predictor of 3-point MACE, non-fatal MI, and non-fatal stroke. The event-free survival rate was significantly lower in the high-risk group compared to that in the low-risk group. Patients with hypertriglyceridemia have obesity and impaired glucose tolerance as background factors. Our study therefore needed to evaluate the prevalence of MetS to assess residual LDL-C risk and compare the incidence of coronary events in patients with or without MetS. The results showed that in patients without MetS, the LDL-window detected an increased risk of a 3-point MACE; however, this was not for patients with MetS. Therefore, in an assessment of coronary lipid risk, non-obese patients with high TG and non-HDL-C levels may have a higher risk of experiencing a MACE.

In addition, Kaplan-Meier survival curve analysis showed that the cumulative incidence of 3-point MACE was significantly different between the 4 groups and significantly

Table 5. Univariate and Multivariate Cox Regression Analyses for 3-Point MACE

	Univariate analysis (n=624)			Multivariable analysis (n=588)		
	HR	95% CI	P value	Adjusted HR	95% CI	P value
Female gender, yes	0.714	0.421–1.210	0.21	0.641	0.356–1.153	0.137
Age, years	1.013	0.987–1.039	0.341	1.018	0.989–1.048	0.227
Current smoker, yes	1.303	0.725–2.311	0.365	1.418	0.770–2.613	0.263
Alcohol intake, yes	0.817	0.534–1.250	0.351	0.951	0.600–1.507	0.830
Exercise, yes	0.621	0.409–0.944	0.026	0.674	0.432–1.050	0.081
BMI, kg/m^2	1.000	0.944–1.060	0.987	0.942	0.877–1.011	0.099
SBP, mmHg	1.015	1.003–1.027	0.017	1.013	0.999–1.026	0.061
DBP, mmHg	1.018	0.999–1.038	0.061	n/a		
Heart rate, beats/min	1.010	0.993–1.027	0.260	1.010	0.991–1.028	0.310
TC, mg/dL	1.000	0.993–1.007	0.996	n/a		
HDL-C, mg/dL	0.986	0.970–1.002	0.094	n/a		
TG, mg/dL	1.001	1.000–1.002	0.122	n/a		
LDL-C, mg/dL	0.999	0.991–1.006	0.730	n/a		
MDA-LDL, U/L	1.004	0.999–1.009	0.118	1.002	0.995–1.009	0.571
Blood sugar, mg/dL	1.005	1.001–1.009	0.019	1.003	0.998–1.008	0.237
Uric acid, mg/dL	0.986	0.837–1.161	0.864	0.943	0.781–1.138	0.538
Lipid risk group						
Low-risk	Ref.			Ref.		
Hyper-TG	1.450	0.930–2.261	0.101	1.355	0.774–2.373	0.287
Hyper-non-HDL	1.930	0.601–6.195	0.268	1.378	0.403–4.710	0.609
High-risk	2.636	1.051–6.613	0.039	3.560	1.230–10.306	0.019
FMD, group						
≥7.0%	Ref.			Ref.		
<7.0%	2.024	1.016–4.029	0.045	2.096	1.034–4.251	0.040
sd-LDL, group						
<24.4 mg/dL	Ref.			Ref.		
≥24.4 mg/dL, <36.4 mg/dL	1.418	0.812–2.477	0.220	1.218	0.663–2.237	0.525
≥36.4 mg/dL	1.859	1.094–3.160	0.021	1.330	0.613–2.886	0.471
Medication for hypertension, yes	1.858	0.682–5.064	0.226	2.728	0.827–8.997	0.099
Medication for dyslipidemia, yes	3.945	1.248–12.473	0.019	4.219	1.312–13.570	0.016
Medication for diabetes mellitus, yes	1.338	0.871–2.054	0.183	1.104	0.653–1.864	0.713

Abbreviations as in Tables 1,2. Low-risk, non-HDL-C <170 mg/dL and TG <150 mg/dL; hyper-TG, non-HDL-C <170 mg/dL and TG ≥150 mg/dL; hyper-non-HDL, non-HDL-C ≥170 mg/dL and TG <150 mg/dL; high-risk, non-HDL-C ≥170 mg/dL and TG ≥150 mg/dL. Missing values (smoker=18, alcohol intake=17, exercise=25, LDL-C=10, and uric acid=1) were excluded from the univariate or multivariable analyses. DBP, TC, TG, LDL, and HDL were not entered into the multivariate analysis to avoid multicollinearity.

higher in the high-risk group compared with that in the low-risk group. Interestingly, in patients with a FMD index ≥7.0%, the cumulative incidence of 3-point MACE was different between the 4 groups and between the high-risk and low-risk groups. In contrast, in patients with a FMD index <7.0%, there was a significant difference between the 4 groups, but not in comparison with each group of the pair. These results suggest that the stratified lipid risk may predict cardiovascular outcomes in patients with CAD and normal vascular endothelial function, but are masked impaired vascular endothelial function. In CAD patients with impaired vascular endothelial function, multifactorial risk beyond dyslipidemia may cause 3-point MACE; therefore, we suggest that it is necessary to target treatment beyond LDL-C in the early stage of CAD before a decrease in FMD occurs. Moreover, in CAD patients with hypertriglyceridemia, if a high-dose statin is insufficient for achieving levels below the target value, more discussion is needed on whether we should further lower LDL or start lowering TG levels.

In the FMD-J study A cohort, 93% of the patients had concomitant dyslipidemia, with 89% of the patients received lipid-lowering medications. However, the type of drug used in the study is unclear. The LDL-C level of the hyper-non-HDL and high-risk groups markedly exceeded >70 mg/dL. In particular, even the medication rate in the hyper-non-HDL group was 100%. The exact usage rate of statin in each group was unclear; thus, we were not able to discuss the required medications for both groups. However, the LDL-C level was higher in the hyper-non-HDL group than in the high-risk group, whereas the TG level was higher in the high-risk group than in the hyper-non-HDL group. As a result, the adjusted HR of 3-point MACE in the high-risk group was significantly the highest. Hence, for the high-risk group, a TG-lowering therapy may be an additional option, along with strict LDL-lowering interventions. The SPPARM-α, pemafibrate, is a novel fibrate developed in Japan to target TG lowering. A recent study in statin-treated patients showed that pemafibrate (0.4 mg/day) reduced TG levels by 50% and increased HDL-C by 13–16%.[20] The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients

with Diabetes (PROMINENT) study assessed the impact of TG lowering with pemafibrate for patients with type 2 diabetes and mild-to-moderate hypertriglyceridemia and low levels of HDL-C.[23] However, the study was discontinued earlier because the intervention was unlikely to reduce the cardiovascular risk. Hence, we may have to wait for other favorable reports of pemafibrate to confirm the secondary prevention of CAD in the future.

Finally, our multivariate regression analysis showed that stratified high lipid risk was a more powerful predictor of the incidence of 3-point MACE than that achieved by high serum levels of sd-LDL. Measurement of sd-LDL is relatively uncommon, whereas TG and non-HDL-C are measured commonly and therefore lipid risk stratification can be easily applied in daily clinical practice. Our sub-analysis demonstrated the validity of lipid risk stratification for predicting cardiovascular events in patients with CAD. Based on our results, we envision that lipid risk stratification-guided treatment for secondary prevention of CAD may be a promising therapeutic strategy.

Potential Limitations

First, the percentage of patients treated for dyslipidemia was lower in the high-risk group compared with that in the other groups. The percentage of statin use as dyslipidemia therapy could not be included in the data analysis, and therefore it is possible there was bias for lipid therapy in our analyses. Second, there was only a low number of patients in the high-risk group compared with the other lipid risk groups. In addition, only a few patients experienced cardiovascular death. As a consequence, these small sample sizes may have been a major limitation in the subanalyses. Third, in the present study, most TG measurements were carried out during the same patient visit in which the FMD index was measured, and this required fasting. However, whether all TG measurements in the study were performed on fasting blood samples remains unclear. Fourth, familial hypercholesterolemia (FH) was not an exclusion criterion in the FMDJ study and therefore, it is possible that some patients with FH were included in the study. Although our study had these potential limitations, we consider our data may be of great value in providing cardiologists with some novel guidelines for enhancing secondary prevention of CAD.

Conclusions

A novel lipid risk stratification, simply using TG and non-HDL-C levels, in combination with FMD measurement, is useful for predicting cardiovascular outcomes in patients with CAD. The findings of our study suggest that lipid risk stratification-guided treatment for secondary prevention of CAD may be a promising therapeutic strategy. Hypertriglyceridemia should be treated in addition to LDL-C lowering therapy, with the objective of further improving the long-term prognosis of CAD patients in the early stage of vascular endothelial dysfunction.

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Disclosures

K. Kario, K. Node, S. Ueda, T. Inoue, H. Ito, and Y. Ohya are members of *Circulation Journal*'s Editorial Board.

Conflict of Interest

S. Koba received contract research funds from Denka Co. Ltd. Y. Higashi received consulting fees related to this study from Mitsubishi Tanabe, as well as honoraria and grants from Teijin, Boehringer Ingelheim, MSD, Sanofi, AstraZeneca, Kyowa Hakko Kirin, Takeda, Astellas, Daiichi Sankyo, Mochida, Nihon Kohden, Shionogi, Nippon Sigmax, Sanwa Kagaku Kenkyusho, Unex, and Kao; and honoraria from Radiometer, Omron, Sumitomo Dainippon, Otsuka, Torii, Kowa, Fujiyakuhin, Amgen, Nippon Shinyaku, Itamar, Bayer, Eli Lilly, and Ono.

IRB Information

The study protocol was approved by the Dokkyo Medical University Independent Ethics Committee (Approval No: 22030). Clinical Trial Registration Information: http://umin.ac.jp; Registration Number for Clinical Trial: UMIN000012950

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-21-1068