Non-Fasting Hypertriglyceridemia as an Independent Risk Factor for Coronary In-Stent Restenosis after Primary Bare Metal Stent Implantation in Patients with Coronary Artery Disease

A Single-Site Retrospective Observational Study

Masayuki Yoshimura,1,2 MD, Seiji Umemoto,3,4 MD, Reo Kawano,3 PhD, Mitsuyuki Hiromoto,5 MD, Michio Yamada,6 MD, Tatsuhiko Fujimura,1 MD, Masakazu Tanaka,7 MD, Tomoko Nao,9 MD, Toshiro Miura,6 MD and Masafumi Yano,1 MD

Summary

After a percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD), in-stent neoatherosclerosis may pose a risk of in-stent restenosis (ISR). To clarify whether non-fasting hypertriglyceridemia contributes to ISR, we examined the relationship between non-fasting hypertriglyceridemia (i.e., triglyceride (TG) level ≥ 200 mg/dL) and ISR after stenting with a bare metal stent (BMS) post-primary PCI in patients with CAD by means of a single-site retrospective analysis. A total of 1,039 patients with CAD were enrolled, and 86 patients (112 lesions) were evaluated for BMS-ISR 3-6 months post-primary PCI. The percentage of patients with non-fasting hypertriglyceridemia was significantly higher in the ISR (+) group than in the ISR (−) group (P < 0.009). The follow-up period and number of patients in the ISR (+) group were significantly smaller than those in the ISR (−) group (P < 0.001). There were no significant between-group differences in the other baseline patient characteristics before the primary PCI or at the time of the follow-up coronary angiography. However, at the follow-up period, the ISR (+) group had significantly lower diastolic blood pressure and high-density lipoprotein cholesterol levels (P = 0.015) and significantly higher TG levels (P = 0.012) than the ISR (−) group. A multiple logistic regression analysis demonstrated that non-fasting hypertriglyceridemia and a follow-up period of ≥ 6 months were independent risk factors for ISR after primary PCI in patients with BMS implantation for stenotic CAD (P = 0.006), with an adjusted odds ratio of 8.232 (1.201-56.410) and 0.006 (95% confidence interval < 0.001-0.045), respectively. Non-fasting hypertriglyceridemia may be an additional independent risk factor for BMS-ISR after primary PCI in patients with CAD.

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P lasma triglyceride (TG) levels correspond to the sum of the TG contents of TG-rich lipoproteins and their remnants. Some uncertainty exists regarding the direct causal role of TG-rich lipoproteins in the progression of atherosclerosis and cardiovascular disease (CVD).1,2,3) Compared with the level of low-density lipoprotein cholesterol (LDL-C) alone, the level of non-high-density lipoprotein cholesterol (non-HDL-C; i.e., the sum of the total cholesterol carried by atherogenic lipoproteins) provides a better indication of the risk of CVDs, including coronary heart disease, particularly in patients with hypertriglyceridemia; this advantage holds true across both fasting and non-fasting conditions.4,5) Although LDL-C < 100 mg/dL remains the primary treatment target to reduce the risk of CVD,6) a number of large-scale epidemiological studies have shown that elevated TG levels are independently associated with an increased incidence of cardiovascular events, even in patients treated effectively with statins.7,8)

In-stent neoatherosclerosis has emerged as an important factor contributing to late vascular complications, including very-late stent thrombosis and late in-stent restenosis (ISR). The development of neoatherosclerosis may occur months to years after the placement of a stent, whereas atherosclerosis in native coronary arteries develops over decades. The mechanisms underlying the rapid development of neoatherosclerosis remain unknown.9) Oi, et al. demonstrated that in patients who have undergone a
successful percutaneous coronary intervention (PCI), a non-fasting increase in the remnant-like particle cholesterol (RLP-C) concentration is an independent risk factor for restenosis, even in patients with normal fasting RLP-C levels. It was also reported that the preprocedural TG/HDL-C ratio in fasting or non-fasting samples could be beneficial for assessments of the risk of ISR.

ISR was reported to occur in as many as 30% of all patients who received a bare metal stent (BMS). In another study, the prevalences of overall restenosis of a BMS during the periods > 30 days /c033 1 year and > 1 year /c033 3 years were reported as 46.9% and 30.6%, respectively; however, the cause(s) of neoatherosclerosis during this relatively early post-procedural period have remained unclear. Despite the advent of drug-eluting stents (DESs) and improved stent designs, the rates of ISR in patients treated with a DES remain as high as 10%. It has also been unclear whether non-fasting hypertriglyceridemia contributes to ISR after a PCI. We conducted the present study to further clarify the relationship between ISR and hypertriglyceridemia. We investigated whether non-fasting hypertriglyceridemia contributes to ISR after a primary PCI in patients implanted with a BMS who underwent a primary PCI due to coronary artery disease (CAD).

**Methods**

**Definitions of acute coronary syndrome, stable and effort angina pectoris, and silent myocardial ischemia:** The definitions of acute coronary syndrome (acute myocardial infarction or unstable angina), stable and effort angina pectoris, and silent myocardial ischemia used in this study were as described previously.

**Patients:** This study was performed as a single-site retrospective observational study. During the period from April 2009 to March 2011, 1,039 patients were admitted to Shuto General Hospital (Yanai, Japan) for further examination of CAD by coronary angiography (CAG) and for the treatment of CAD. 356 patients with CAD underwent a PCI.
after the primary PCI, or a PCI was performed for a new lesion for which a DES was first placed for the primary coronary lesion; patients with cancer; and patients whose PCI was unsuccessful due to chronic total occlusion (CTO). The total number of excluded patients was 201.

Of the 155 remaining patients, 68 patients were excluded due to a target vessel diameter of < 3.0 mm, including 3 patients with CTO and 1 patient who had undergone a balloon angioplasty. Thus, 86 patients with CAD with 112 lesions with a target vessel diameter of ≥ 3.0 mm and BMS implantation in a coronary artery were evaluated for ISR, including the following: 55 patients with acute coronary syndrome (73 lesions), 15 patients with stable angina pectoris (17 lesions), and 16 patients with silent myocardial ischemia (22 lesions).

**Definition of non-fasting hypertriglyceridemia and lipoprotein analysis:** To measure the lipid profile both at the time of each patient’s primary PCI and during the follow-up CAG performed 3 and 6 months after the primary PCI, blood samples from all enrolled patients were taken in the morning before each CAG after overnight fasting and later the same day, 3-4 hours after lunch with a routine hospital meal (i.e., non-fasting-state). The timing for the non-fasting blood collection (3-4 hours after the meal) was determined based on a previous study. In cases of acute coronary syndrome, 24 hours after the termination of heparinization during the hospitalization, the first blood sampling was collected by the same method as for follow-up CAG. On the other hand, in the elective PCI case, it was performed by the same method as for follow-up CAG to avoid the effects of heparinization on serum lipid levels. All patients consumed a hospital meal with a similar composition in the same hospital at the time of the primary PCI and during the follow-up CAG. For all patients, blood sampling was performed before the CAG prior to the primary PCI and as part of the follow-up CAG examinations at 3 and 6 months.

Dyslipidemia was treated according to the secondary prevention guidelines for the prevention of atherosclerotic cardiovascular diseases by the patient’s attending physician. Throughout the study period, any lipid-lowering drugs or other medications that could influence plasma lipid levels were essentially unchanged. This decision was made at the discretion of the attending physicians and was not required by the present prospective study’s protocol. Any observation of lipid abnormalities in a patient (LDL-C < 100 mg/dL, HDL-C > 40 mg/dL, and TG < 150 mg/dL according to the guidelines) was addressed with only diet and exercise intervention; no additional drugs were prescribed to control lipid abnormalities. All blood samples were measured in the central laboratory of Shuto General Hospital. Serum cholesterol and TG levels were measured using the enzymatic method. HDL-C was determined using direct measurement.

Although the assessment of non-fasting TG levels is not standardized and the reference range has not been determined, several studies have indicated that non-fasting or random TG exceeding the usual fasting cut-off point (≥ 150 mg/dL) is independently associated with increased atherosclerotic CVD risk, and TG levels ≥ 200 mg/dL may indicate a substantial increase in the risk of atherosclerotic CVD. Blood samples typically measured after an 8- to 12-hour fast have been the standard for assessing the plasma lipid profile. However, the maximal mean changes at 1-6 hours after habitual meals were considered clinically insignificant at +26 mg/dL for TGs. A recent American Heart Association (AHA) statement on hypertriglyceridemia and CAD suggests that clinicians can use a non-fasting TG level of ≥ 200 mg/dL to identify a “hypertriglyceridemic state” and then follow up the patient with a fasting TG level if it is deemed necessary. In the present study, based on the AHA statement on TGs and CVD, we defined non-fasting hypertriglyceridemia as a TG level of ≥ 200 mg/dL after admission for a primary PCI for each coronary culprit lesion, whether or not the patient was fasting.

**Definition of chronic kidney disease (CKD):** The definition of CKD is an estimated glomerular filtration rate (eGFR) of < 60 mL per minute per 1.73 m² or the presence of urinary protein. In our patients, the eGFR was estimated using a modified Modification of Diet in Renal Disease formula adapted for the Japanese population.

**Quantitative CAG, PCI, and study protocol:** A quantitative CAG examination was performed in all patients before the primary PCI and at follow-up. After an intracoronary injection of isosorbide dinitrate, the luminal coronary diameters of both the stenotic lesions and reference sites were evaluated in the coronary arteries. The luminal coronary diameter was determined by consensus agreement among four experienced interventional cardiologists who had no knowledge of the lipid data. Luminal coronary stenosis ≥ 75% was a significant or “culprit” lesion, and a primary PCI was then performed using the usual procedure. When the outcome of balloon angioplasty was not satisfactory (e.g., insufficient luminal gain, coronary dissection, hazziness, or elastic recoil), intracoronary BMS implantation was additionally performed in the culprit lesions.

Essentially all of the patients underwent follow-up CAG at 3 and 6 months after the primary PCI according to a serial angiographic follow-up study designed to evaluate the temporal mode of lumen diameter changes after BMS implantation; however, since the present study had a retrospective design, the timing of the serial regular follow-up CAG after the primary PCI was not strictly decided by the attending physicians; rather, the timing was determined based on the patient’s desire and availability and a consultation with the attending physician. In each case, the coronary diameters at both the stenotic lesions and reference sites before, immediately after, and at 3 and 6 months after the primary PCI were evaluated as mentioned above.

Our hospital is in a city in the suburban area of Japan’s main island, Honshu Island. During the study period, the BMSs were implanted for both elective and emergency PCIs to some extent (especially in cases of CAD without complex stenotic lesions) because the intervention team staff of our hospital was more cautious and conservative regarding the use of DESs considering the safety and efficacy of DESs for Japanese patients.

We defined restenosis of the ISR as a > 50% loss of the initial luminal gain by stent implantation achieved by
PCI compared with the control reference vessel diameter achieved by the PCI. The minimal lumen diameter, the late loss (i.e., the change in the minimum lumen diameter of the target stenosis from post-dilation to follow-up), and the loss index (the ratio of late loss to acute gain) were measured by a quantitative CAG analysis before and immediately after angioplasty.

At our hospital during the period of this study, intravascular ultrasound was routinely performed to exclude stent failure, as we always wanted to make sure that the stent implantation was appropriately performed (following the patient’s informed consent) prior to the follow-up CAG, which also included an intravascular ultrasound procedure. The actual geometric changes of the minimal luminal diameter, late loss, and loss index at the BMS implantation sites were evaluated by intravascular ultrasound at both the 3- and 6-month follow-ups. If significant stent restenosis was observed at the 3-month follow-up, a second PCI was planned for the treatment of the lesion(s) with significant restenosis, and the patient was then withdrawn from the study’s 6-month follow-up.

Selection of BMS implantation cases: We selected BMS implantation cases and excluded DES implantation cases in this study to avoid several biases for neoatherosclerotic lesions by hypertriglyceridemia following stent implantation. The reasons for this were as follows. First, the effects of the drugs eluted from the DES indwelling in the lesion or eluted from vascular lesions other than the DES-indwelling lesion (such as distal lesions), especially when a DES is indwelling in a proximal lesion, are unknown. Second, at the time that the data were collected for this study, BMSs were the main stents used for stent implantation in the treatment of coronary artery lesions, and DESs were used only in limited cases as a secondary treatment for restenotic lesions, e.g., for highly calcified lesions in dialysis patients, coronary artery diameter < 3.0 mm, or for lesions that were longer and more diffuse compared with the present cases. Thus, the data obtained following DES implantation may have been biased by the selection of the DES for the specific coronary lesions. It is also important to note that there have been several reports concerning the postprandial lipid profile and neoatherosclerosis, and in the present study, these data were collected at both the primary PCI and during the follow-up period in a relatively large PCI sample.

Ethics committee procedure and consent: Written informed consent from the patients was waived because of the retrospective nature of this study, although we gave public notice regarding the implementation of the research, including the handling of existing information. All participants were provided opportunities to withdraw consent, and patients who requested omission from the study were excluded. The study was conducted in accordance with the Declaration of Helsinki. The research protocol, including the informed-consent waiver form, was approved by the institutional review boards of Yamaguchi University Hospital and Shuto General Hospital.

Statistical analyses: For continuous variables, results are presented as the mean ± SD or medians (interquartile ranges), and the differences between groups with and without ISR were evaluated using t-test or Mann-Whitney U-test. Categorical variables are reported as counts and percentages and compared with Fisher’s exact test. The mixed-effects logistic regression model with patient-specific random effects was used to assess the contribution of non-fasting hypertriglyceridemia to the incidence of ISR after primary PCI. The following variables were initially incorporated into the univariate model: age, sex, body mass index, smoking habit, drinking habit, diabetes, diagnosis of acute coronary syndrome, stent length, stent diameter, non-fasting hypertriglyceridemia, changes from the pre-primary PCI value for systolic and diastolic blood pressure, HDL-C, LDL-C, triglyceride, non-HDL-C, and blood glucose.

We also analyzed the time points of the measurements and obtained the median values at 6 months post-PCI as the threshold values; we then added the values of the categorical variables at < 6 months to the covariates of the analysis model. Since this was a retrospective observational study, the timing of the serial regular follow-up CAG after the primary PCI was not strictly decided by the attending physicians. Variables that were revealed as significant in the multivariate model by backward elimination were subsequently included in a new model. All statistical analyses were conducted using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). Probability (P)-values < 0.05 were considered significant.

Results

Baseline patient characteristics and dimensions of the BMSs used for the treatment of culprit lesions: Table I summarizes the baseline patient characteristics of the ISR (+) and ISR (−) groups. The patients’ ages were significantly higher in the ISR (+) group than in the ISR (−) group, so was the percentage of patients with non-fasting hypertriglyceridemia. The follow-up period in the ISR (+) group was significantly shorter than that in the ISR (−) group, and the number of patients in the ISR (+) group was significantly greater than that in the ISR (−) group. The other indices shown in Table I are not significantly different between the groups.

Table II provides the brands and dimensions (diameter and length) of the BMSs used for the treatment of the culprit lesions in the ISR (+) and ISR (−) groups. Little difference in these parameters was seen between the two groups. Although the minimal luminal diameter and the acute gain were not significantly different between the two groups, the late loss at both the 3- and 6-month follow-ups and the loss index were significantly greater in the ISR (+) group than in the ISR (−) group for lesion treatment in the patients with and without BMS-ISR after their primary PCI.

Profile of blood pressure, fasting lipid profile, and blood glucose levels in the ISR (+) and ISR (−) groups before the primary PCI and at the follow-up CAG: Table III summarizes the blood pressure values, fasting lipid profile, and blood glucose levels in the ISR (+) and ISR (−) groups before the primary PCI and at the follow-up CAG. There were few notable differences in blood pressure, lipid profiles, or blood glucose levels between the two groups before the primary PCI, whereas at the follow-
The results of our present retrospective analysis of 86 patients (112 lesions) demonstrated that non-fasting hypertriglyceridemia may be an independent risk factor for BMS-ISR in patients with stent implantation by a primary PCI for CAD. In our cohort, the LDL-C level was well controlled for the secondary prevention of CAD after stent implantation according to the Japan Atherosclerosis Soci-

Table I. Baseline Characteristics of Patients with and Without In-Stent Restenosis (ISR) of a Bare-Metal Stent (BMS) by Primary Percutaneous Coronary Intervention (PCI)

| Variable                                      | ISR (+) (n = 24) | ISR (-) (n = 62) | P-value |
|-----------------------------------------------|------------------|------------------|---------|
| Male, n (%)                                   | 17 (70.8)        | 48 (77.4)        | 0.580†  |
| Age, mean ± SD                                | 73 ± 10          | 67 ± 11          | 0.018†  |
| BMI, median (IQR)                             | 24.6 (21.0–26.7) | 24.2 (22.2–26.4)| 0.802†  |
| Smoking habit, n (%)                          | 13 (54.2)        | 34 (54.8)        | 1.000†  |
| Drinking habit, n (%)                         | 8 (36.4)         | 22 (38.6)        | 1.000†  |
| Non-fasting hypertriglyceridemia, n (%)       | 17 (70.8)        | 24 (38.7)        | 0.009†  |
| Follow-up period, months, median (IQR)        | 3.0 (3.0–5.5)    | 6.0 (6.0–7.0)    | < 0.001†|
| < 6 months, n (%)                             | 18 (75.0)        | 2 (3.2)          |         |
| ≥ 6 months, n (%)                             | 6 (25.0)         | 60 (96.8)        |         |
| Diagnosis of CAD, n (%)                       |                  |                  | 0.969†  |
| ACS                                           | 15 (62.5)        | 40 (64.5)        |         |
| AP                                            | 4 (16.7)         | 9 (14.5)         |         |
| SMI                                           | 5 (20.8)         | 11 (17.7)        |         |
| Effort AP                                      | 0 (0.0)          | 2 (3.2)          |         |
| Diagnosis of CAD, n (%)                       |                  |                  | 1.000†  |
| ACS                                           | 15 (62.5)        | 40 (64.5)        |         |
| Stable AP                                     | 9 (37.5)         | 22 (35.5)        |         |
| Dyslipidemia, n (%)                           | 15 (62.5)        | 42 (67.7)        | 0.800†  |
| Statin                                        | 14 (58.3)        | 37 (59.7)        | 1.000†  |
| Fibrates                                      | 0 (0.0)          | 4 (6.5)          | 0.573†  |
| Ezetimibe                                     | 0 (0.0)          | 0 (0.0)          | –       |
| Diabetes, n (%)                               | 8 (33.3)         | 24 (38.7)        | 0.804†  |
| Oral hypoglycemic agents                      | 3 (12.5)         | 15 (24.2)        | 0.375†  |
| Insulin                                       | 1 (4.2)          | 2 (3.2)          | 1.000†  |
| CKD, n (%)                                    | 10 (41.7)        | 23 (37.1)        | 0.806†  |
| Hypertension, n (%)                           | 23 (95.8)        | 58 (93.5)        | 1.000†  |
| ACEI/ARB                                      | 19 (79.2)        | 46 (74.2)        | 0.782†  |
| Nitrates                                      | 6 (25.0)         | 24 (38.7)        | 0.315†  |
| β-blocker                                     | 8 (33.3)         | 14 (22.6)        | 0.409†  |
| CCB                                           | 11 (45.8)        | 29 (46.8)        | 1.000†  |
| Diuretics                                     | 9 (37.5)         | 14 (22.6)        | 0.182†  |
| Hyperuricemia, n (%)                          | 4 (16.7)         | 7 (11.3)         | 0.491†  |
| Family history of cerebrocardiovascular disease, n (%) | 19 (79.2)        | 52 (83.9)        | 0.752†  |
| Lesion number, mean ± SD                     | 1.3 ± 0.7        | 1.3 ± 0.6        | 0.644†  |

ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AP, angina pectoris; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; IQR, interquartile range; and SMI, silent myocardial ischemia. Diuretics were prescribed for the treatment of hypertension, but not for the treatment of heart failure. †Fisher’s exact test, ‡t-test, §Mann–Whitney U-test.

up, the ISR (+) group showed significantly lower diastolic blood pressure and HDL-C levels and significantly higher TG levels than the ISR (−) group. Note that the LDL-C level was < 100 mg/dL in both groups at the follow-up, and no significant difference in LDL-C was observed between the two groups.

Risk factors for ISR after PCI: We then performed a mixed-effects logistic regression model analysis to assess the relative contributions among the risk factors shown in Tables I, II, III. The results of the analysis shown in Table IV demonstrate that the presence of non-fasting hypertriglyceridemia and the TG level were significant independent risk factors for ISR after PCI with stent implantation for stenotic CAD, with odds ratios (ORs) of 4.085 (95% confidence interval [CI]: 1.530–10.908) for non-fasting hypertriglyceridemia (defined as TG > 200 mg/dL), 1.007 (95% CI: 1.001–1.012) for the TG level, and 0.009 (0.002-0.048) for the follow-up period of ≥ 6 months.

Finally, since the patient age and the follow-up period were significantly higher in the ISR (+) group (Table I), we further adjusted for age using the backward elimination method (Table V). The results of the analysis clearly demonstrated that non-fasting hypertriglyceridemia and a follow-up period of ≥ 6 months were significant and independent risk factors with adjusted ORs of 8.232 (95% CI: 1.201–56.410) and 0.006 (95% CI: < 0.001–0.045), respectively, for ISR in patients with CAD treated with a primary PCI with BMS implantation.

Discussion

The results of our present retrospective analysis of 86 patients (112 lesions) demonstrated that non-fasting hypertriglyceridemia may be an independent risk factor for BMS-ISR in patients with stent implantation by a primary PCI for CAD. In our cohort, the LDL-C level was well controlled for the secondary prevention of CAD after stent implantation according to the Japan Atherosclerosis Soci-
However, our present findings suggest that non-fasting hypertriglyceridemia as a residual risk factor after statin therapy may be involved in the pathogenesis of BMS-ISR after a primary PCI.

In-stent neatherosclerosis is histologically characterized by an accumulation of lipid-laden foamy macrophages with or without either or both necrotic core formation and calcification within the neointima in the months to years following stent placement. The mechanisms responsible for this accelerated in-stent neatherosclerosis are responsible for this accelerated in-stent neatherosclerosis.

### Table II. Stent Brand and Dimensions Used for Lesion Treatment in Patients with or Without In-Stent Restenosis (ISR) of a Bare Metal Stent (BMS) After Percutaneous Coronary Intervention (PCI)

| Variable                  | ISR (+) (n = 33) | ISR (-) (n = 79) | P-value |
|---------------------------|------------------|------------------|---------|
| Stent name, n (%)         | 16 (48.5)        | 31 (39.2%)       | 0.617† |
| Driver                    |                  |                  |         |
| Liberte                   | 7 (21.2)         | 12 (15.2%)       | -       |
| ML-VISION                 | 7 (21.2)         | 25 (31.6%)       | -       |
| ML-Zeta                   | 0 (0.0)          | 1 (1.3%)         | -       |
| S-stent                   | 2 (6.1)          | 9 (11.4%)        | -       |
| VISION                    | 1 (3.0)          | 1 (1.3%)         | -       |
| Stent diameter, mm, median (IQR) |                   |                  |         |
| 3.0                       | 19 (57.6)        | 42 (53.2)        | 0.113² |
| 3.5                       | 11 (33.3)        | 17 (21.5)        | -       |
| 4.0                       | 3 (9.1)          | 20 (25.3)        | -       |
| Stent length, mm, median (IQR) | 18.0 (18.0–24.0) | 18.0 (15.0–24.0) | 0.69⁰ |
| MLD, mm, n (%)            | 16.3 (21.2)      | 25 (31.6%)       | -       |
| 3.0                       | 19 (57.6)        | 42 (53.2)        | 0.113² |
| 4.0                       | 3 (9.1)          | 20 (25.3)        | -       |
| 3.5                       | 11 (33.3)        | 17 (21.5)        | -       |
| Acute gain, mm, median (IQR) | 3.0 (2.7–3.5)    | 3.0 (2.7–3.5)    | 0.75⁶   |
| Late loss at 3-month follow-up period, mm, median (IQR) | 2.3 (1.6–2.7)   | 0.8 (0.8–1.0)  | < 0.001¹ |
| Late loss at 6-month follow-up period, mm, median (IQR) | 1.2 (0.9–1.4)   | 0.8 (0.8–1.0)  | 0.016⁴ |
| Late loss index, median (IQR) | 0.8 (0.5–0.9)   | 0.3 (0.3–0.3)   | < 0.001¹ |

The stent length, minimum lumen diameter, acute gain, late loss, and late loss index used for the treatment of culprit lesions by PCI are shown as median (interquartile range: IQR). ISR indicates in-stent restenosis; and MLD, minimum lumen diameter. ¹Fisher’s exact test, ²Mann–Whitney U-test.

### Table III. Blood Pressure, Non-Fasting Lipid Profiles, and Blood Glucose in Patients with or Without In-Stent Restenosis (ISR) of a Bare Metal Stent (BMS) Before Primary Percutaneous Coronary Intervention (PCI) and at Follow-Up Coronary Angiography (CAG)

| Primary PCI | ISR (+) (n = 24) | ISR (-) (n = 62) | P-value |
|-------------|------------------|------------------|---------|
| Systolic BP, mmHg | 128.0 (118.5–150.5) | 144.0 (123.0–164.0) | 0.350 |
| Diastolic BP, mmHg | 68.5 (59.5–77.5) | 72.0 (64.0–87.0) | 0.135 |
| HDL-cholesterol, mg/dL | 47.1 (36.1–54.6) | 47.1 (40.4–57.6) | 0.590 |
| LDL-cholesterol, mg/dL | 108.4 (92.5–130.6) | 109.1 (94.4–136.7) | 0.958 |
| Triglyceride, mg/dL | 120.5 (96.5–180.5) | 113.0 (89.0–181.0) | 0.765 |
| Non-HDL cholesterol, mg/dL | 145.4 (112.6–166.4) | 140.6 (116.8–163.7) | 0.950 |
| Blood glucose, mg/dL | 110.0 (103.5–160.5) | 128.0 (102.0–153.0) | 0.506 |
| Creatinine, mg/dL | 0.9 (0.7–1.1) | 0.9 (0.7–1.0) | 0.333 |
| eGFR, mL/minute/1.73 m² | 62.1 (40.8–72.6) | 67.3 (54.6–81.1) | 0.077 |
| Follow-up CAG |               |                  |         |
| Systolic BP, mmHg | 136.0 (129.5–153.5) | 148.0 (128.0–161.0) | 0.383 |
| Diastolic BP, mmHg | 64.0 (56.0–75.5) | 71.5 (64.0–80.0) | 0.015 |
| HDL-cholesterol, mg/dL | 39.8 (35.2–50.6) | 49.3 (41.1–56.9) | 0.015 |
| LDL-cholesterol, mg/dL | 91.2 (70.4–103.7) | 91.9 (73.0–117.5) | 0.281 |
| Triglyceride, mg/dL | 172.5 (131.0–237.5) | 135.5 (95.0–187.0) | 0.012 |
| Non-HDL cholesterol, mg/dL | 131.3 (118.5–149.7) | 126.2 (103.7–149.4) | 0.424 |
| Blood glucose, mg/dL | 132.5 (106.5–158.0) | 118.5 (105.0–153.0) | 0.399 |
| Creatinine, mg/dL | 0.9 (0.8–1.3) | 0.9 (0.7–1.0) | 0.572 |
| eGFR, mL/minute/1.73 m² | 65.5 (46.1–76.1) | 63.9 (50.8–74.1) | 0.974 |

All data are median (interquartile range: IQR). The timing for non-fasting blood collection (3–4 h after a meal) was determined based on a previous study. ¹⁰ BP indicates blood pressure; CAG, coronary angiography; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ISR, in-stent restenosis; LDL, low-density lipoprotein; and PCI, percutaneous coronary intervention.
are likely to involve dysfunctional endothelial coverage of the stented segment.\(^{16}\) TG-rich lipoproteins are also thought to directly contribute to intimal cholesterol deposition and are involved in the activation and enhancement of several proinflammatory, proapoptotic, and procoagulant pathways.\(^{17}\) TG-rich lipoproteins are likely to involve dysfunctional endothelial coverage of the stented segment. 24) TG-rich lipoproteins are also shown to promote endothelial dysfunction, which potentiates atherogenesis.\(^{11}\) These mechanisms may synergistically facilitate in-stent neoatherosclerosis after a PCI in patients with CAD.\(^{13}\)

In 2014, it was reported that although statin-based standard therapy can ameliorate the risk of CVD complications,\(^{15}\) patients remain at high risk of cardiovascular events due to the pandemics of obesity, metabolic syndrome, and type 2 diabetes.\(^{20}\) The Residual Risk Reduction Initiative highlighted atherogenic dyslipidemia, defined as an imbalance between proatherogenic TG-rich apolipoprotein B-containing lipoproteins and antiatherogenic apolipoprotein A-I lipoproteins (as in HDL), as an important modifiable contributor to lipid-related residual cardiovascular risk.\(^{20}\) Although hypertriglyceridemia can be an independent genetic disorder, TG levels that are even moderately elevated (\(\geq 150\) mg/dL) may identify individuals at risk for insulin resistance syndrome with or without diabetes,\(^{20}\) and such levels are also commonly associated with a procoagulant state and hypertension.\(^{15}\)

In addition, similar to low HDL-C, high serum TG may act synergistically with other lipid abnormalities to increase the atherosclerotic CVD risk. The non-fasting TG level may be an equally or more potent atherosclerotic CVD risk factor than fasting TG.\(^{25}\) Our present investigation revealed that the LDL-C level in the follow-up period was \(< 100\) mg/dL in both the ISR (+) and ISR (−) groups; there was no significant between-group difference in the LDL-C level. The multiple logistic regression analysis demonstrated that only non-fasting hypertriglyceridemia was an independent risk factor for BMS-ISR after primary PCI in this study population.

The monitoring of non-HDL-C provides a simple,

### Table IV. Mixed-Model Analysis of the Risk Factors for In-Stent Restenosis (ISR) of a Bare Metal Stent (BMS) in Patients with or Without ISR After Primary Percutaneous Coronary Intervention (PCI)

| Variable                              | OR (95% CI)   | P-value |
|---------------------------------------|---------------|---------|
| Age                                   | 1.041 (0.996–1.088) | 0.081  |
| Sex, male                             | 1.285 (0.435–3.792) | 0.651  |
| BMI                                   | 1.004 (0.880–1.144) | 0.957  |
| Smoking habit                         | 1.402 (0.553–3.554) | 0.478  |
| Drinking habit                        | 1.149 (0.444–2.970) | 0.776  |
| Diabetes                              | 1.062 (0.408–2.766) | 0.903  |
| Diagnosis of ACS                      | 1.107 (0.405–3.024) | 0.843  |
| Stent length                          | 1.012 (0.928–1.103) | 0.789  |
| Stent diameter 3.5 mm                 | 1.055 (0.370–3.009) | 0.920  |
| Stent diameter 4.0 mm                 | 0.362 (0.089–1.483) | 0.161  |
| Follow-up period ≥ 6 months           | 0.009 (0.002–0.048) | 0.001  |
| Non-fasting hypertriglyceridemia      | 4.085 (1.530–10.908) | 0.006  |
| Δ Systolic BP                         | 1.004 (0.988–1.021) | 0.632  |
| Δ Diastolic BP                        | 1.009 (0.979–1.040) | 0.575  |
| Δ HDL-cholesterol                     | 0.965 (0.920–1.013) | 0.151  |
| Δ LDL-cholesterol                     | 0.998 (0.984–1.012) | 0.765  |
| Δ Triglyceride                        | 1.007 (1.001–1.012) | 0.016  |
| Δ Non-HDL cholesterol                 | 1.012 (0.998–1.026) | 0.085  |
| Δ Blood glucose                       | 1.002 (0.996–1.007) | 0.591  |

\(\Delta\) Indicates the difference in non-fasting lipid values before primary PCI and at follow-up coronary angiography. A mixed-model was used for the analysis, with “individual” as a random effect. ACS indicates acute coronary syndrome.

### Table V. Mixed-Model Analysis of Risk Factors for In-Stent Restenosis (ISR) of a Bare Metal Stent (BMS) in Patients with or Without BMS-ISR After Primary Percutaneous Coronary Intervention (PCI)

| Variable                              | OR (95% CI)   | P-value |
|---------------------------------------|---------------|---------|
| Age                                   | 0.995 (0.920–1.076) | 0.902  |
| Non-fasting hypertriglyceridemia      | 8.232 (1.201–56.410) | 0.034  |
| Follow-up period ≥ 6 months           | 0.006 (0.001–0.045) | 0.001  |

Non-fasting triglyceride, Δtriglyceride, follow-up period, and age were used for adjustment of the mixed-model analysis, and the results were selected using the backward elimination method.
practical tool for treatment decisions regarding the management of patients’ lipid-related residual cardiovascular risk.\textsuperscript{29} However, the results of our present analyses revealed that non-fasting hypertriglyceridemia may be a more potent risk factor than non-HDL-C for ISR after statin therapy and stent implantation in patients with dyslipidemia and CAD. Although we did not evaluate small-dense LDL or RLPs, Koba, \textit{et al.} performed an oral fat tolerance test in patients with acute myocardial infarction, and their results showed that the postprandial (non-fasting) increase of large very-low-density lipoprotein fractions and RLPs contributes to the formation of small-dense LDL in patients with CAD, and high concentrations of both small-dense LDL and RLPs and postprandial hyperlipidemia are recognized as risk factors for CAD.\textsuperscript{28} Koba, \textit{et al.} also showed that small-dense LDL is strongly associated with various types of CAD, independent of traditional and nontraditional coronary risk factors.\textsuperscript{29}

Ohi, \textit{et al.} examined the influence of a postprandial increase in the remnant lipoprotein concentration on the development of restenosis after PCI, and they reported that although the mean concentrations of RLP-C and RLP-TG were normal in the fasting state, a postprandial change in the RLP-C concentration was a significant and independent risk factor for restenosis after PCI.\textsuperscript{10} Our present findings are compatible with their results, demonstrating that the measurement of non-fasting hypertriglyceridemia may be more effective than that of non-HDL-C for assessing the risk of BMS-ISR after successful PCI. Miyazaki, \textit{et al.} assessed the lipid profiles, plasma cholesterol ester transfer activity, and in-stent intimal hyperplasia after treatment with fenofibrate (one of the peroxisome proliferator-activated receptor-\(\alpha\) agonists) in patients who underwent elective coronary stenting, and their observations indicated that fenofibrate inhibited the cholesterol ester transfer activity and thereby improved the patients’ atherogenic lipoprotein profiles after coronary stenting.\textsuperscript{10} In that study, the reduction of cholesterol ester transfer activity was significantly correlated with an increase in the LDL particle size and a decrease in the content of TGs in large HDL subclasses and with the inhibition of neointimal hyperplasia.\textsuperscript{30}

At our hospital, we routinely perform follow-up CAG to examine whether significant stent restenosis has occurred at roughly 3 and 6 months after the first stent implantation.\textsuperscript{22} In this patient series, if significant stent restenosis was observed at the first follow-up CAG, a second PCI was planned for the treatment of the restenosis lesion, and the patient was withdrawn from the study. Therefore, the ISR (+) group showed more cases with significant stent restenosis at the first follow-up CAG and had shorter follow-up periods (<6 months; median, 3 months) than the ISR (−) group (≥6 months; median, 6 months) as shown in Table I.

Few data are available to evaluate the involvement of CKD in BMS-ISR, even though the postprandial TG level has been reported to be independently linked to both CKD and insulin resistance.\textsuperscript{31} Although our present study was a retrospective observational analysis, the incidences of CKD and hyperuricemia were scarcely different between the ISR (+) and ISR (−) groups.

\textbf{Study limitations:} The present study has several limitations. First, it was a single-site retrospective study with a relatively small number of patients \((n = 86)\). For this reason, we cannot exclude the possibility of residual confounders that may have influenced the results. Second, regarding non-fasting blood sampling, the influence of the patients’ dietary intake and its content and the time between blood collections and dietary intake were not precisely adjusted, although standard meals for patients with CAD were provided to all the study patients. Third, non-fasting hypertriglyceridemia was diagnosed based on the blood sampling value of only the CAG at the primary PCI and the first and second follow-up CAG, and we did not measure biomarkers, such as HbA1c or the abdominal circumference to assess metabolic syndrome, insulin to evaluate insulin resistance, or remnant lipoprotein cholesterol or small-dense or oxidized LDL,\textsuperscript{32,33} which have been reported as relevant to secondary prevention in patients with CAD.\textsuperscript{34,35}

In addition, although the prevalence of an alcohol habit (one of the major risk factors for hypertriglyceridemia) was not significantly different between the two patient groups, there may be several additional reasons for the higher TG levels in the ISR(+) group, such as lower levels of exercise or excessive calorie intake.\textsuperscript{36} The blood pressure and LDL-C values at the follow-up did not reach the target levels according to the current guidelines for secondary prevention, as this study was an analysis of the treatment data obtained by the cardiologists in charge of routine daily medical care at our hospital. Our findings may indicate that more intensive treatment will be required for the patients as secondary prevention.\textsuperscript{37}

Finally, in this study, we evaluated the relationship between non-fasting hypertriglyceridemia and ISR in patients with CAD to further clarify the mechanisms underlying the development of neoatherosclerosis after BMS implantation. The effects of non-fasting hypertriglyceridemia on ISR after the implantation of a DES in patients with CAD should also be explored, although it has been reported that the rate of ISR in BMS implantation is around 30%.\textsuperscript{12} whereas that in DES is no higher than 10%.\textsuperscript{12} In summary, the present findings need to be tested and expanded in future studies with larger numbers of patients.

\textbf{Conclusion}

The results of our analyses demonstrated that non-fasting hypertriglyceridemia was an independent risk factor for the development of BMS-ISR after primary PCI in patients with CAD. However, it remains to be determined in future studies whether either or both dietary and pharmacological intervention to reduce non-fasting hypertriglyceridemia can reduce the risk of BMS-ISR after primary PCI in patients with CAD. Based on our present findings, we believe that for patients who have achieved the target LDL-C levels with statin therapy according to the guidelines for secondary prevention and for high-risk patients even for primary prevention, the measurement of the non-fasting TG level may be the most useful approach in routine check-ups of the lipid profile at outpatient cli-
ics by a general physician or cardiologist for evaluation of the residual risk control.

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Disclosure

Conflicts of interest: None.

References

1. Rosenson RS, Davidson MH, Hirsh BJ, Kathiresan S, Gaudet D. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. J Am Coll Cardiol 2014; 64: 2525-40.
2. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res 2016; 118: 547-63.
3. Toth PP. Triglyceride-rich lipoproteins as a causal factor for cardiovascular disease. Vasc Health Risk Manag 2016; 12: 171-83.
4. Iso H, Naito Y, Sato S, et al. Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol 2001; 153: 490-9.
5. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007; 298: 299-308.
6. Nakamura K, Miyoshi T, Yunoki K, Ito H. Postprandial hyperlipidemia as a potential residual risk factor. J Cardiol 2016; 67: 335-9.
7. Teramoto T, Sasaki J, Ishibashi S, et al. Diagnosis of atherosclerosis. Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the diagnosis and prevention of atherosclerotic cardiovascular Diseases in Japan-2012 Version. J Atheroscler Thromb 2014; 21: 296-8.
8. Reith C, Armitage J. Management of residual risk after statin therapy. Atherosclerosis 2016; 245: 161-70.
9. Oi K, Shimokawa H, Hirakawa Y, et al. Postprandial increase in plasma concentrations of remnant-like particles: an independent risk factor for restenosis after percutaneous coronary intervention. J Cardiovasc Pharmacol 2004; 44: 66-73.
10. Kundi H, Korkmaz A, Balun A, et al. In-stent restenosis after a successful coronary stent implantation due to stable angina associated with TG/HDL-C ratio? Angiology 2017; 68: 816-22.
11. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999; 100: 1872-8.
12. Kuntz RE, Baim DS. Defining coronary restenosis. Newer clinical and angiographic paradigms. Circulation 1993; 88: 1310-23.
13. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic research Consortium-2 consensus document. Eur Heart J 2018; 39: 2192-207.
14. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: A report of the American College of Cardiology/American Heart Association task force on clinical data stan-
15. dards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol 2015; 66: 403-69.
16. Kinoshita M, Yokote K, Arai H, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular Diseases 2017. J Atheroscler Thromb 2018; 25: 846-984.
17. Teramoto T, Sasaki J, Ishibashi S, et al. Coronary artery disease. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan–2012 version. J Atheroscler Thromb 2014; 21: 86-92.
18. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points–a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J 2016; 37: 1944-58.
19. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 123: 2292-333.
20. Driver SL, Martin SS, Glueck TJ, Clary JM, Blumenthal RS, Stone NJ. Fasting or nonfasting lipid measurements: it depends on the question. J Am Coll Cardiol 2016; 67: 1227-34.
21. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982-92.
22. Kinura T, Nosaka H, Yokoi H, Ibawuchi M, Nobuyoshi M. Serial angiographic follow-up after Palmaz-Schatz stent implantation: comparison with conventional balloon angioplasty. J Am Coll Cardiol 1993; 21: 1557-63.
23. Lansky AJ, Popma J. Qualitative Angiography. 3rd ed. WB Saunders; 1999.
24. van den Berg MJ, van der Graaf Y, de Borst GJ, et al. Low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B and cardiovascular risk in patients with manifest arterial disease. Am J Cardiol 2016; 118: 804-10.
25. Fruchart JC, Davignon J, Hermans MP, et al. Residual macrovascular risk in 2013: what have we learned? Cardiovasc Diabetol 2014; 13: 26.
26. Nakamura A, Monna Y, Kajitani S, et al. Different postprandial lipid metabolism and insulin resistance between non-diabetic patients with and without coronary artery disease. J Cardiol 2015; 66: 435-44.
27. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017; 23: 1-87.
28. Koba S, Hirano T, Morayama S, et al. Small dense LDL phenotype is associated with postprandial increases of large VLDL and remnant-like particles in patients with acute myocardial infarction. Atherosclerosis 2003; 170: 131-40.
29. Koba S, Hirano T, Kondo T, et al. Significance of small dense low-density lipoproteins and other risk factors in patients with various types of coronary heart disease. Am Heart J 2002; 144: 1026-35.
30. Miyazaki T, Shimada K, Miyauchi K, et al. Effects of fenofibrate on lipid profiles, cholesterol ester transfer activity, and initial intimal hyperplasia in patients after elective coronary stenting. Lipids Health Dis 2010; 9: 122.
31. Saland JM, Satlin LM, Zalsos- Johnson J, Cremers S, Ginsberg HN. Impaired postprandial lipemic response in chronic kidney disease. Kidney Int 2016; 90: 172-80.
32. Hiki M, Shimada K, Ohmura H, et al. Serum levels of remnant lipoprotein cholesterol and oxidized low-density lipoprotein in patients with coronary artery disease. J Cardiol 2009; 53: 108-16.
33. Nakamura A, Monna Y, Kajitani S, et al. Effect of glycemic
state on postprandial hyperlipidemia and hyperinsulinemia in patients with coronary artery disease. Heart Vessels 2016; 31: 1446-55.

34. Tani S, Matsumoto M, Nagao K, Hirayama A. Association of triglyceride-rich lipoproteins-related markers and low-density lipoprotein heterogeneity with cardiovascular risk: effectiveness of polyacrylamide-gel electrophoresis as a method of determining low-density lipoprotein particle size. J Cardiol 2014; 63: 60-8.

35. Nakamura T, Takano H, Umetani K, et al. Remnant lipoproteinemia is a risk factor for endothelial vasomotor dysfunction and coronary artery disease in metabolic syndrome. Atherosclerosis 2005; 181: 321-7.

36. Koba S, Hirano T, Yoshino G, et al. Remarkably high prevalence of small dense low-density lipoprotein in Japanese men with coronary artery disease, irrespective of the presence of diabetes. Atherosclerosis 2002; 160: 249-56.

37. Nishikura T, Koba S, Yokota Y, et al. Elevated small dense low-density lipoprotein cholesterol as a predictor for future cardiovascular events in patients with stable coronary artery disease. J Atheroscler Thromb 2014; 21: 755-67.

38. Kugiyama K, Doi H, Takazoe K, et al. Remnant lipoprotein levels in fasting serum predict coronary events in patients with coronary artery disease. Circulation 1999; 99: 2858-60.