Target of Triglycerides as Residual Risk for Cardiovascular Events in Patients With Coronary Artery Disease — Post Hoc Analysis of the FMD-J Study A —

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Background: Circulating triglyceride (TG) levels are a current focus as a residual risk for cardiovascular (CV) events. We evaluated the relationship between circulating TG levels and future CV events in patients with coronary artery disease (CAD) who were treated with conventional therapy.

Methods and Results: We analyzed data for 652 patients who were enrolled in the FMD-J Study A. We investigated the associations between serum TG levels and first major CV events (death from CV cause, nonfatal acute coronary syndrome (ACS), nonfatal stroke, and CAD) for a 3-year follow-up period. Patients were divided into 4 groups based on serum TG level: low-normal (<100 mg/dL), high-normal (100–149 mg/dL), borderline hypertriglyceridemia (150–199 mg/dL), and moderate hypertriglyceridemia (≥200 mg/dL). During a median follow-up period of 46.6 months, 14 patients died (9 from CV causes), 16 had nonfatal ACS, 6 had nonfatal stroke, and 54 had CAD. The Kaplan-Meier curves for first major CV event among the 4 groups were significantly different (P=0.04). After adjustment for various confounders, serum TG level ≥100 mg/dL were significantly associated with an increased risk of first major CV events compared with serum TG level <100 mg/dL.

Conclusions: Serum TG level may be a surrogate marker for predicting CV events in patients with CAD.

Key Words: Atherosclerosis; Cardiovascular events; Triglycerides

n elevated serum level of low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for cardiovascular (CV) disease.1–4 Although the benefits of LDL-C lowering on CV events are well established, patients with dyslipidemia still have a high residual risk of such events.5,6 Several lines of evidence have shown a link between serum triglyceride (TG) levels and CV dis-
ease. However, there are conflicting results regarding the association between elevated serum TG levels and the incidence of CV events.

In the guidelines for cholesterol management, serum TG levels <150 mg/dL are defined as normal. Some clinical studies have shown that reducing TG levels by treatment with fibrates reduces CV events in a subgroup of patients with high TG levels. Unfortunately, there is insufficient evidence available to determine optimal TG levels for prevention of CV events. Klempfner et al reported that high-normal TG levels (100–150 mg/dL) are associated with an increased risk of all-cause death. We previously showed that endothelial function is already impaired even in subjects with serum TG levels of 106–131 mg/dL after adjustment for various confounders. However, it is unclear whether patients with high-normal TG levels have an increased risk of CV events. The purpose of this study was to evaluate the relationship between circulating TG levels, especially high-normal TG levels, and future CV events in patients with coronary artery disease (CAD) who were treated with conventional therapy including LDL-C lowering treatment.

Methods

Study Design

The rationale and design of the FMD-J Study A have been described previously. It was a prospective multicenter observational cohort study conducted at 22 university hospitals and affiliated clinics in Japan to examine the usefulness of flow-mediated vasodilation assessment for the management of patients with CAD with a 3-year follow-up period. The study was approved by the ethical committee of each institute and was executed in accordance with the Good Clinical Practice guidelines. All subjects gave written informed consent for participation in the study. The protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000012950).

Study Subjects

Between May 1, 2010 and August 31, 2012, a total of 679 patients aged 30–88 years who had been diagnosed with CAD were enrolled in the FMD-J Study A. CAD was defined as myocardial infarction, angina pectoris with organic stenosis of at least 1 coronary artery confirmed by diagnostic imaging (coronary angiography, cardiac nuclear scintigraphy, or coronary computed tomography), or previous percutaneous coronary intervention. The exclusion criteria were as follows: a history of coronary bypass surgery; severe valvular heart disease; arrhythmia that required treatment (i.e., atrial fibrillation, atrial flutter; permanent pacemaker implantation or frequent ventricular premature beats); severe chronic heart failure (New York Heart Association level >Level III); malignancy; undergoing treatment with steroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs; a serum creatinine level ≥2.5 mg/dL; a history of stroke, aortic disease (except peripheral artery disease), or serious liver disease; and judgement of the attending physician that the individual was ineligible for inclusion in the study.

Study Procedures

Blood examinations were conducted at the start of the study and CV events were monitored annually during the 3-year follow-up period. The participants were managed by their attending physicians, who were encouraged to treat any CV risk factors, including hypertension, dyslipidemia and diabetes mellitus, to achieve the best available standard of care in accordance with guidelines.

Measurement of Blood Samples and Assessment of CV Risk Factors

The subjects were instructed to abstain from eating, drinking alcohol, smoking and consuming caffeine for at least 12 h prior to the study. Venous blood samples were obtained from the left antecubital vein. Levels of serum total cholesterol, TGs, and high-density lipoprotein cholesterol (HDL-C) were enzymatically measured (JCA-BM6010). LDL-C was calculated by the Friedewald formula. We excluded patients with serum TG levels ≥400 mg/dL. Non-HDL-C was calculated by the following formula: total cholesterol – HDL-C. Small dense LDL-C (sdLDL-C) was measured by the method previously described. Glucose levels were measured by the glucose oxidase immobilized oxygen electrode method (GA08II; A&T, Yokohama, Japan). Hyperension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least 3 different occasions in a seated position, or currently taking antihypertensive medication. Diabetes mellitus was identified.
Table 1. Clinical Characteristics of the Subjects on the Basis of Serum Triglyceride Levels (mg/dL)

| Variable                        | Total (n=652) | <100 (n=264) | 100–149 (n=188) | 150–199 (n=104) | ≥200 (n=96) | P value for trend |
|--------------------------------|--------------|--------------|----------------|----------------|------------|------------------|
| Age, years                     | 64±8         | 66±8         | 64±9           | 62±9           | 62±8       | <0.001           |
| Sex, male/female               | 545/107      | 216/48       | 156/32         | 88/16          | 85/11      | 0.46             |
| BMI, kg/m²                      | 24.8±3.6     | 24.0±3.6     | 25.1±3.5       | 25.5±4.0       | 25.8±3.1   | <0.001           |
| SBP, mmHg                       | 129±17       | 129±17       | 131±17         | 129±16         | 128±16     | 0.53             |
| DBP, mmHg                       | 75±11        | 74±11        | 76±11          | 75±10          | 74±11      | 0.23             |
| Heart rate, beats/min           | 67±12        | 66±11        | 67±12          | 66±11          | 68±14      | 0.52             |
| Medical history, n (%)          |              |              |                |                |            |                  |
| Hypertension                    | 613 (94)     | 243 (92)     | 180 (96)       | 102 (98)       | 88 (92)    | 0.053            |
| Dyslipidemia                    | 610 (94)     | 232 (88)     | 178 (95)       | 104 (100)      | 96 (100)   | <0.001           |
| Diabetes mellitus               | 243 (37)     | 100 (38)     | 66 (35)        | 38 (37)        | 39 (41)    | 0.82             |
| Smoker                          | 87 (14)      | 26 (10)      | 28 (15)        | 14 (14)        | 19 (20)    | 0.08             |
| Previous MI                     | 308 (47)     | 116 (44)     | 94 (50)        | 48 (46)        | 50 (52)    | 0.44             |
| Previous angina pectoris        | 333 (51)     | 142 (54)     | 91 (48)        | 56 (54)        | 44 (46)    | 0.44             |
| Vasoactive angina               | 31 (5)       | 14 (5)       | 10 (5)         | 3 (3)          | 4 (4)      | 0.73             |
| Laboratory data                 |              |              |                |                |            |                  |
| Total cholesterol, mg/dL        | 170±30       | 164±27       | 166±33         | 177±30         | 182±31     | <0.001           |
| Triglycerides, mg/dL            | 131±66       | 75±16        | 122±14         | 171±13         | 256±47     | <0.001           |
| HDL-C, mg/dL                    | 51±13        | 56±14        | 48±11          | 47±12          | 43±10      | <0.001           |
| LDL-C, mg/dL                    | 93±27        | 93±23        | 94±30          | 96±28          | 87±30      | 0.11             |
| sdLDL-C, mg/dL                  | 33±14        | 25±9         | 31±11          | 41±15          | 48±13      | <0.001           |
| Ratio of sdLDL-C to LDL-C       | 0.36±0.15    | 0.27±0.07    | 0.34±0.10      | 0.44±0.12      | 0.56±0.17  | <0.001           |
| Non-HDL-C, mg/dL                | 119±29       | 108±24       | 119±30         | 130±28         | 138±28     | <0.001           |
| Glucose, mg/dL                  | 117±35       | 114±29       | 115±29         | 119±37         | 127±50     | 0.01             |
| HbA1c, %                        | 6.4±1.0      | 6.3±0.9      | 6.4±1.0        | 6.5±1.2        | 6.7±1.2    | 0.15             |
| High-sensitivity CRP, mg/dL      | 0.10±0.14    | 0.09±0.14    | 0.11±0.16      | 0.09±0.10      | 0.12±0.15  | 0.24             |
| Medications, n (%)              |              |              |                |                |            |                  |
| Antiplatelets                   | 620 (95)     | 252 (95)     | 176 (94)       | 98 (94)        | 94 (98)    | 0.37             |
| Antihypertensive therapy        | 600 (92)     | 239 (91)     | 176 (94)       | 98 (94)        | 87 (91)    | 0.48             |
| Calcium-channel blockers        | 317 (49)     | 125 (47)     | 97 (52)        | 58 (56)        | 37 (39)    | 0.07             |
| Renin-angiotensin system inhibitors | 443 (68) | 169 (64)     | 132 (70)       | 72 (69)        | 70 (73)    | 0.32             |
| β-blockers                      | 292 (45)     | 117 (44)     | 83 (44)        | 48 (46)        | 44 (46)    | 0.98             |
| Diuretics                       | 77 (12)      | 33 (13)      | 24 (13)        | 11 (11)        | 9 (9)      | 0.80             |
| Any lipid modification therapy  | 577 (88)     | 228 (86)     | 172 (91)       | 92 (88)        | 85 (89)    | 0.40             |
| Statins                         | 541 (83)     | 214 (81)     | 159 (85)       | 88 (85)        | 80 (83)    | 0.75             |
| Fibrates                        | 13 (2)       | 7 (3)        | 3 (2)          | 2 (2)          | 1 (1)      | 0.74             |
| Eicosapentaenoic acids          | 42 (6)       | 15 (6)       | 19 (10)        | 5 (5)          | 3 (3)      | 0.09             |
| Ezetimibe                        | 46 (7)       | 22 (8)       | 10 (5)         | 5 (5)          | 9 (9)      | 0.37             |
| Antihyperglycemic therapy       | 199 (31)     | 82 (31)      | 58 (31)        | 32 (31)        | 27 (28)    | 0.96             |
| Insulin-dependent               | 38 (6)       | 18 (7)       | 14 (7)         | 3 (3)          | 3 (3)      | 0.19             |
| Framingham risk score, %        | 12.4±7.5     | 10.9±6.4     | 12.7±8.3       | 12.8±7.7       | 15.6±7.4   | <0.001           |
| FMD, %                          | 4.7±2.8      | 4.5±2.8      | 4.6±2.5        | 4.9±2.8        | 5.1±3.4    | 0.26             |

All results are presented as mean±SD. BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FMD, flow-mediated vasodilation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; sdLDL-C, small dense low-density lipoprotein cholesterol.

using the American Diabetes Association criteria. Dyslipidemia was identified using the Third Report of the National Cholesterol Education Program. We defined smokers as those who were current smokers. The Framingham risk score was calculated by points of risk factors: age, total cholesterol level, HDL-C level, systolic blood pressure, and smoking status.

Measurement of Flow-Mediated Dilation (FMD)
A high-resolution ultrasonography (UNEXEF18G, UNEX Co, Nagoya, Japan) was used to evaluate FMD. The protocol for measurement of FMD has been described in detail. Briefly, the longitudinal image of the brachial artery was assessed before and after generation of a vascular response to reactive hyperemia induced by a 5-min period of forearm occlusion to evaluate FMD. FMD was defined as the maximal percentage change in vessel diameter from the baseline value.
CV Outcomes

All CV events were reported annually from each institution to the Efficacy Endpoint Review Committee. An independent clinical events committee adjudicated the endpoints of death from CV causes, nonfatal acute coronary syndrome (ACS), nonfatal stroke, CAD, hospitalization for heart failure, and death from any cause.\(^1\) CAD was defined as coronary artery restenosis or de novo coronary artery stenosis, confirmed by diagnostic imaging (coronary angiography, cardiac nuclear scintigraphy, or coronary computed tomography). Definitions of the clinical outcomes have been provided previously.\(^1\) The committee, consisting of members blinded to any information with regard to blood samples, assessed the appropriateness of clinical judgments of CV events according to prespecified criteria. The committee could request physicians to provide additional clinical information on CV events if needed. Any differences in opinion under assessment were resolved by discussion, and the committee finally determined whether the CV event would be included as an outcome event in the analysis. We first assessed the associations of serum TG levels with first major CV event (death from CV cause, nonfatal ACS, nonfatal stroke, and CAD) and then we assessed the associations with death from CV causes, nonfatal ACS, nonfatal stroke, CAD, hospitalization for heart failure, and death from any cause.

Statistical Analysis

Results are presented as mean±SD for continuous variables and as percentages for categorical variables. Statistical significance was set at a level of P<0.05. Continuous variables were compared by using ANOVA for multiple groups. Categorical variables were compared by means of the χ² test. Relations between variables were determined by Pearson’s correlation analysis. Time-to-event endpoint analyses were performed by the Kaplan-Meier method. We categorized subjects into 4 groups according to the serum TG level: low-normal (<100 mg/dL), high-normal (100–149 mg/dL), borderline hypertriglyceridemia (150–199 mg/dL), moderate hypertriglyceridemia (≥200 mg/dL). A log-rank test was used to compare survival in the groups. We evaluated the associations between serum TG levels and first major CV events after adjustment for age, sex, and CV risk factors by using Cox’s proportional hazard regression analysis. As the sensitivity analysis, we performed exploratory analysis to evaluate the prognostic value of serum TG levels before and after adjustment for age and sex. In the second sensitivity analysis, the proportional hazards assumption was confirmed by inspection of Schoenfeld residuals and log-log plotting. The data was processed using the software package stata version 9 (Stata Co., College Station, TX, USA).

Results

Baseline Clinical Characteristics

Of the 679 patients, complete outcome data were available for 652 and their baseline characteristics are summarized in Table 1. Of the 652 patients, 545 (84%) were men and 107 (16%) were women. Mean levels of total cholesterol, TGs, HDL-C, and LDL-C were 170±30 mg/dL, 131±66 mg/dL, 51±13 mg/dL, and 93±27 mg/dL, respectively. Of the 652 patients, 613 (94%) had hypertension, 610 (94%) had dyslipidemia, 243 (37%) had diabetes mellitus, and 87 (14%) were current smokers. Among the patients, 777 (88%) were being treated with lipid-lowering agents, and 541 (83%) of the patients were on statins, 13 (2%) were on fibrates, 42 (6%) were on eicosapentaenoic acids, and 46 (7%) were on ezetimibe.

Relationships Between Serum TG Levels and CV Risk Factors

Participants were categorized into 4 groups based on serum TG levels (Table 1). Body mass index, total cholesterol, sDLLD-L-C, ratio of sdLDL-C to LDL-C, non-HDL-C, glucose, and Framingham risk score were significantly increased and age and HDL-C were significantly decreased with an increase in serum TG level. There were significant differences in the prevalence of hypertension and prevalence of dyslipidemia among the 4 groups. There were significant relationships of serum TG levels with sdLDL-C, ratio of sdLDL-C to LDL-C, non-HDL-C, and HDL-C. Serum TG levels did not correlate with LDL-C (Table 2).

Serum TG Levels and CV Events

During a median follow-up period of 46.6 months (interquartile range, 40.9–54.6 months), 14 patients died (9 from CV causes), 16 had nonfatal ACS, 6 had nonfatal stroke, 54 had CAD, and 5 had hospitalization for heart failure (Table 3). The Kaplan-Meier curves for first major CV event among the 4 groups according to serum TG level (P=0.04; Figure 1A) and ratio of sdLDL-C to LDL-C (P=0.02; Supplementary Figure 1A) were significantly different, but there were no significant differences between the Kaplan-Meier curves for first major CV event among the 4 groups according to LDL-C (P=0.97; Figure 1B), HDL-C (P=0.15; Supplementary Figure 1B), non-HDL-C (P=0.49; Supplementary Figure 1C), and sdLDL-C (P=0.46; Supplementary Figure 1D). Clinical characteristics and clinical outcomes of the patients on the basis of LDL-C are summarized in Supplementary Table 1 and Supplementary Table 2. The Kaplan-Meier curves for CAD among the 4 groups were significantly different (P=0.04), but the Kaplan-Meier curves for death from CV disease (P=0.18), nonfatal ACS (P=0.06), nonfatal stroke (P=0.98), hospitalization

### Table 2. Univariate Analysis of Relationships Between Serum Triglyceride Levels and Variables

| Variables                     | r   | P value |
|-------------------------------|-----|---------|
| Age, years                    | −0.18 | <0.001  |
| BMI, kg/m²                    | 0.20 | <0.001  |
| SBP, mmHg                     | −0.03 | 0.44    |
| DBP, mmHg                     | 0.03 | 0.50    |
| Heart rate, beats/min         | 0.04 | 0.27    |
| Total cholesterol, mg/dL      | 0.21 | <0.001  |
| HDL-C, mg/dL                  | −0.37 | <0.001  |
| LDL-C, mg/dL                  | −0.07 | 0.09    |
| sdLDL-C, mg/dL                | 0.60 | <0.001  |
| Ratio of sdLDL-C to LDL-C     | 0.71 | <0.001  |
| Non-HDL-C, mg/dL              | 0.39 | <0.001  |
| Glucose, mg/dL                | 0.14 | <0.001  |
| HbA1c, %                      | 0.10 | 0.04    |
| High-sensitivity CRP, mg/dL    | 0.06 | 0.14    |
| Framingham risk score, %      | 0.21 | <0.001  |
| FMD, %                        | 0.07 | 0.09    |

Univariate analysis of the relationship between serum triglyceride levels and variables (Pearson’s correlation analysis). Abbreviations as in Table 1.
Serum TG levels are associated with metabolic disorders that contribute to the pathogenesis of CV disease.8,26-27 It has been shown that serum TG levels are associated with other lipid levels, especially HDL-C.8,28,29 In the present study, we confirmed that serum TG levels significantly correlated with age, body mass index, total cholesterol, HDL-C, sdLDL-C, ratio of sdLDL-C to LDL-C, non-HDL-C, and glucose. In the present study, after adjustment for CV risk factors, elevated serum TG levels were significantly associated with an increased risk of first major CV event compared with serum TG levels of <100mg/dL (Table 4).

### Discussion

In the present study, we demonstrated that elevated serum TG levels were significantly associated with an increased risk of the incidence of first major CV events in patients with CAD who were treated with conventional therapy. Multivariate regression analysis revealed that even high-normal TG levels from 100 to 149mg/dL were associated with the incidence of first major CV events in these patients. These findings suggest that we should pay attention to high-normal TG levels as well as to high TG levels in order to prevent CV events. Serum TG levels may be a surrogate marker for prediction of CV events.

Table 3: Clinical Outcomes of the Subjects on the Basis of Serum Triglyceride Levels (mg/dL)

| Variable, n (%) | Total (n=652) | <100 (n=264) | 100–149 (n=188) | 150–199 (n=104) | ≥200 (n=96) | P value for trend |
|----------------|-------------|-----------|---------------|---------------|-------------|------------------|
| First major cardiovascular event | 82 (12.6) | 21 (8.0) | 30 (16.0) | 16 (15.4) | 15 (15.6) | 0.03 |
| Death from cardiovascular disease | 9 (1.4) | 2 (0.8) | 5 (2.7) | 0 (0) | 2 (2.1) | 0.12 |
| Nonfatal acute coronary syndrome | 16 (2.5) | 4 (1.5) | 2 (1.1) | 5 (4.8) | 5 (5.2) | 0.06 |
| Nonfatal stroke | 6 (0.9) | 2 (0.8) | 2 (1.1) | 1 (1.0) | 1 (1.0) | 0.99 |
| Coronary artery disease | 54 (8.3) | 13 (4.9) | 23 (12.2) | 10 (9.6) | 8 (8.3) | 0.04 |
| Hospitalization for heart failure | 5 (0.8) | 3 (1.1) | 0 (0) | 1 (1.0) | 1 (1.0) | 0.33 |
| Death from any cause | 14 (2.1) | 6 (2.3) | 6 (3.2) | 0 (0) | 2 (2.1) | 0.15 |

All results are presented as number (%). First major cardiovascular events included death from cardiovascular disease, nonfatal acute coronary syndrome, nonfatal stroke, and coronary artery disease.
Figure 2. Kaplan-Meier curves of cumulative event-free survival of death from cardiovascular causes (A), nonfatal acute coronary syndrome (B), nonfatal stroke (C), coronary artery disease (D), hospitalization for heart failure (E), and death from any cause (F), according to the serum triglyceride levels.
CV events in patients with low LDL-C but not in those with high LDL-C.\(^{10,11}\) In addition, a previous study showed that serum TG levels predict both long-term and short-term CV risk in patients with ACS who are treated with statins.\(^{33}\) Interestingly, Miller et al showed that the combination of LDL-C level <70 mg/dL and TG level <150 mg/dL was associated with a low risk of CV events compared with LDL-C level ≥70 mg/dL, TG level ≥150 mg/dL, or both.\(^{33}\) These findings suggest that lowering TGs with control of LDL-C may be effective to reduce future CV events. In the present study, 88% of the patients received lipid-lowering therapy and had a mean LDL-C value of 93 mg/dL. We confirmed that elevated serum TG levels were significantly associated with first CV events in patients with CAD who received conventional therapy. Management of serum TG levels is recommended in patients with CAD. As exploratory analysis in a subgroup, we evaluated the association between serum TG levels and first CV events in patients with strictly controlled LDL-C levels. In that study, 110 of the 652 patients had LDL-C levels <70 mg/dL. We categorized patients into 2 groups according to the median serum TG level: a low group (<113 mg/dL) and a high group (≥113 mg/dL). First major CV events occurred in 17 patients. There was no significant difference between the Kaplan-Meier curves for first major CV events (P = 0.17; Supplementary Figure 3). Further studies are required to confirm the relationship between serum TG levels and first CV events in patients with strictly controlled LDL-C levels.

Several lines of evidence have shown an independent association between elevated serum TG levels and CV events.\(^{5,18}\) Studies have shown that fibrates reduce the incidence of CV events in a subgroup of patients with elevated TGs.\(^{13,14,34,35}\) Unfortunately, there is insufficient evidence available to determine optimal TG levels in order to prevent CV events.\(^{32}\) A scientific statement by the American Heart Association suggested that the optimal serum TG level may be <100 mg/dL.\(^{9}\) Recently, we have shown that endothelial function is already impaired in subjects with serum TG levels of 106–131 mg/dL, after adjustment of various confounders including HDL-C.\(^{14}\) In the present study, the prevalence of first major CV events was significantly higher in patients with serum TG levels ≥100 mg/dL than in patients with serum TG levels <100 mg/dL. The results of our study indicated a significant association between serum TG levels ≥100 mg/dL and residual risk in patients with CAD who are receiving conventional therapy. Future studies in a large population are needed to confirm the optimal target level of TGs for prevention of CV events and to determine whether lowering TG levels to the optimal target level reduces CV events.

**Study Limitations**

First, we measured serum TG levels only once when the patients were enrolled. Repeated measurements of serum TG may be more useful as a surrogate marker of future CV events. Second, in the present study, serum levels of LDL-C were not associated with the incidence of first major CV events. There are some possible reasons for this result. The prevalence of dyslipidemia and the level of glucose were significantly higher in patients with LDL-C levels <76 mg/dL.\(^{10}\) (Supplementary Table 1). These CV risk factors may affect the relationship between LDL-C and the risk of CV events. We previously reported that endothelial function was significantly correlated with levels of LDL-C in subjects not receiving statin therapy but not in subjects receiving statin therapy.\(^{36}\) In the present study, more than 80% of the patients in the study groups were on statin therapy. We cannot deny the possibility that cholesterol-lowering therapy using statins hinders the effects of raw values of LDL-C on CV events.

In conclusion, a serum TG level ≥100 mg/dL was independently associated with the incidence of CV events in patients with CAD. Levels of TGs should be considered more seriously as a future target to reduce CV events.

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**Disclosures**

None.

**Clinical Trial Registration Information**

URL for Clinical Trial: http://UMIN; Registration Number for Clinical Trial: UMIN000012950

**References**

1. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. J Ath-

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**Table 4. Association Between Serum Triglyceride Levels (mg/dL) and First Major Cardiovascular Events During Follow-up**

| Variable Triglycerides, mg/dL | Unadjusted† HR (95% CI) P value | Adjusted‡ HR (95% CI) P value | Adjusted§ HR (95% CI) P value | Adjusted|| HR (95% CI) P value | Adjusted‡ HR (95% CI) P value | Adjusted§ HR (95% CI) P value | Adjusted|| HR (95% CI) P value |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| <100                          | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      | 1 (Ref.)                      |
| 100–149                       | 2.12 (1.22–3.75)              | 2.18 (1.26–3.86)              | 2.11 (1.19–3.83)              | 2.07 (1.14–3.83)              | 2.07 (1.14–3.75)              | 2.01 (1.09–3.69)              | 2.08 (1.13–3.80)              |
| 150–199                       | 1.96 (1.01–3.74)              | 2.09 (1.07–4.00)              | 2.25 (1.12–4.44)              | 2.17 (1.07–4.34)              | 2.32 (1.14–4.70)              | 2.25 (1.06–4.76)              | 2.22 (1.11–4.45)              |
| ≥200                          | 2.04 (1.05–3.95)              | 2.25 (1.15–4.41)              | 2.38 (1.18–4.78)              | 2.36 (1.14–4.91)              | 2.50 (1.23–5.07)              | 2.38 (1.04–5.43)              | 2.32 (1.12–4.84)              |

* Adjusted for age, sex. † Adjusted for age, sex, BMI, SBP, LDL-C, glucose and current smoking. ‡ Adjusted for age, sex, BMI, SBP, LDL-C, glucose, current smoking, TG level, and residual risk in patients with CAD. § Adjusted for age, sex, BMI, SBP, small dense LDL-C, glucose and current smoking, CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143–3421.

3. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129(Suppl 2):S1–S45.

4. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al; Authors/Task Force Members; Additional Contributor. 2016 ESC/ESA guidelines for the management of dyslipidaemias. Eur Heart J 2016; 37:2999–3058.

5. Reiner Z. Hypertriglyceridaemia and risk of coronary artery disease. Nat Rev Cardiol 2017; 14: 401–411.

6. Kajikawa M, Maruhashi T, Hida E, Iwamoto Y, Matsumoto T, Iwamoto A, et al. A combination of FMD and nitroglycerine-induced vasodilatation is more effective for prediction of cardiovascular events. Hypertension 2016; 67:1045–1052.

7. Bitzur R, Cohen H, Kamary Y, Shaish A, Harats D, Triglycerides and HDL cholesterol: Stars or second leads in diabetes? Diabetes Care 2009; 32(Suppl 2): S373–S377.

8. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of statin therapy in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol 2015; 65: 2267–2275.

9. Miller M, Stone NJ, Ballantyne C, Bittner, Y, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2011; 123: 2292–2333.

10. Kajikawa M, Maruhashi T, Hida E, Iwamoto Y, Matsumoto T, Iwamoto A, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: Twenty-two-year follow-up of the bezafibrate infarction prevention study and registry. Circ Cardiovasc Qual Outcomes 2016; 9: 100–108.

11. Kajikawa M, Maruhashi T, Matsui K, Iwamoto Y, Iwamoto A, Oda N, et al. Relationship between serum triglyceride levels and endothelial function in a large community-based study. Atherosclerosis 2016; 259: 70–75.

12. Teramoto T, Sasaki I, Ishibashi S, Birou S, Daida H, Dohi S, et al. Treatment B) drug therapy: 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 2013; 20: 850–860.

13. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiiuchi M, et al; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the management of hypertension (JSH 2014). Hypertens Res 2014; 37: 253–390.

14. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, et al. Japanese clinical practice guideline for diabetes 2016. J Diabetes Investig. doi:10.1111/jdi.12810.

15. Fuku LM, Fujimura M, Ohira M, Hirano T. Development of a homogeneous assay for measurement of small dense LDL cholesterol. Clin Chem 2011; 57: 57–65.

16. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care 2017; 40(Suppl 1): S11–S24.

17. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 1987; 59: 91G–94G.

18. Kajikawa M, Maruhashi T, Hida E, Iwamoto Y, Matsumoto T, Iwamoto A, et al. A combination of FMD and nitroglycerine-induced vasodilatation is more effective for prediction of cardiovascular events. Hypertension 2016; 67:1045–1052.

19. Bonsal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 2007; 298: 309–316.

20. West KM, Ahuja MM, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH, et al. The role of circulating glucose and triglyceride concentrations and their interactions with other “risk factors” as determinants of arterial disease in nine diabetic population samples from the WHO multinational study. Diabetes Care 1983; 6: 361–369.

21. Bitzur R, Cohen H, Kamary Y, Shaish A, Harats D, Triglycerides and HDL cholesterol: Stars or second leads in diabetes? Diabetes Care 2009; 32(Suppl 2): S373–S377.

22. Liu J, Wang W, Wang M, Sun J, Liu J, Li Y, et al. Impact of diabetes, high triglycerides and low HDL cholesterol on risk for ischemic cardiovascular disease varies by LDL cholesterol level: A 15-year follow-up of the Chinese Multi-provincial Cohort Study. Diabetes Res Clin Pract 2012; 96: 217–224.

23. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol 2015; 65: 2267–2275.

24. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008; 51: 724–730.

25. Bun N, Foote C, Lvy J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. Lancet 2010; 375: 1875–1884.

26. Bezafrile Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Circulation 2006; 102: 21–27.

27. Matsui S, Kajikawa M, Hida E, Maruhashi T, Iwamoto Y, Iwamoto A, et al. Optimal target level of low-density lipoprotein cholesterol for vascular function in statin naïve individuals. Sci Rep 2017; 7: 8422.

28. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 1987; 59: 91G–94G.