

Association Between the Level of Low-Density Lipoprotein Cholesterol and Coronary Atherosclerosis in Patients Who Have Undergone Coronary Computed Tomography Angiography

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Abstract

Background: Although the Japan Atherosclerosis Society Guidelines 2017 recommend lower levels of low-density lipoprotein cholesterol (LDL-C, < 70 mg/dL or ≤ 100 mg/dL) to prevent secondary cardiovascular events, we cannot conclude that a low level of LDL-C prevents primary cardiovascular events in patients with suspected coronary artery disease (CAD).

Methods: We registered 1,016 patients who were clinically suspected to have CAD and who underwent coronary computed tomography angiography (CCTA) for screening of coronary atherosclerosis. We excluded 350 patients who were receiving anti-lipidemic therapies and finally analyzed 666 patients. The patients were divided into three groups according to the LDL-C level: < 70 mg/dL (n = 25, Low LDL-C), 70 - 99 mg/dL (n = 141, Middle LDL-C), and ≥ 100 mg/dL (n = 500, High LDL-C). A ≥ 50% coronary stenosis was initially diagnosed as CAD, and the number of significantly stenosed coronary vessels (VD), Gensini score and coronary artery calcification (CAC) score were quantified.

Results: There were no significant differences in age, high-density lipoprotein cholesterol, rates of hypertension, hemoglobin A1c, blood sugar or systolic blood pressure among the Low, Middle and High LDL-C groups. On the other hand, there were significant differences in rates of males, smoking, dyslipidemia and diabetes, diastolic blood pressure and triglyceride among the groups. The preva-

lence of CAD values in the Low, Middle and High LDL-C groups were similar, at 52%, 47%, and 46%, respectively. In addition, there were no significant differences in the number of VD, Gensini score or CAC score among the Low LDL-C, Middle LDL-C and High LDL-C groups.

Conclusions: We showed that the level of LDL-C was not associated with the presence or severity of CAD, which indicates that we need to screen by CCTA to prevent primary coronary events even if patients without anti-lipidemic therapies show low levels of LDL-C.

Keywords: Low-density lipoprotein cholesterol; Coronary artery disease; Coronary computed tomography angiography; Gensini score

Introduction

The incidence of atherosclerotic cardiovascular disease (ASCVD) is high when low-density lipoprotein cholesterol (LDL-C) and/or triglyceride (TG) levels are high and/or when the high-density lipoprotein cholesterol (HDL-C) level is low [1-5]. According to the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2017 [6], the management target for LDL-C for primary prevention in patients with low, moderate and high coronary risk should be < 160 mg/dL, < 140 mg/dL and < 120 mg/dL, respectively. Moreover, the target LDL-C for secondary prevention in patients with a history of coronary artery disease (CAD) is < 100 mg/dL. For patients who have high-risk conditions, such as familial hypercholesterolemia, acute coronary syndrome or diabetes complicated by other high-risk conditions, the target LDL-C is < 70 mg/dL.

We have been studying the Coronary Computed Tomography Angiography (FU-CCTA) Registry at Fukuoka University in Japan and have identified coronary risk factors for the primary prevention of CAD [7-16]. In this Registry, none of the patients were diagnosed with CAD until the time of CCTA because we used CCTA to screen for CAD. When patients had significant coronary stenosis as assessed by CCTA, they were

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initially diagnosed with CAD.

Therefore, using the FU-CCTA Registry, we hypothesized that the target LDL-C level for primary prevention of coronary events in patients should be < 70 mg/dL or < 100 mg/dL.

Materials and Methods

Study subjects

One thousand sixteen consecutive subjects who were clinically suspected of having CAD or who had at least one cardiac risk factor (aging, gender male, hypertension (HTN), dyslipidemia (DL), diabetes mellitus (DM), smoking, obesity, family history of CAD and/or chronic kidney disease (CKD)) underwent CCTA. Suspected CAD is defined as having some chest symptoms and/or electrocardiogram (ECG) abnormalities. All subjects underwent CCTA between 2012 and 2019. Patients with creatinine > 2.0 mg/dL or contrast-induced allergy did not undergo multidetector computed tomography (MDCT). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital (#09-10-02), and all subjects gave their written informed consent to participate.

Evaluation of coronary stenosis using CCTA

We evaluated coronary stenosis using CCTA as previously described [7-9]. Patients were assessed by 64-MDCT on an Aquilion 64 (TOSHIBA, Tokyo, Japan) or by 320-MDCT on an Aquilion ONE ViSION (TOSHIBA, Tokyo, Japan). Overall, 15 coronary artery segments were assessed in all patients. Narrowing of the normal contrast-enhanced lumen to $\geq 50\%$ that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant stenosis [17]. The narrowing of the normal contrast-enhanced lumen to $\geq 70\%$ was also defined as significant stenosis. When patients had significant coronary stenosis, they were initially diagnosed with CAD. In addition, in all patients, the severity of CAD was assessed in terms of the number of significantly stenosed coronary vessels (VD) and the Gensini score [18]. The coronary artery calcification (CAC) score was defined on CT images as the presence of more than two contiguous pixels with greater than 130 Hounsfield units. The CAC score in each lesion was then computed by the Agatston method [19].

Evaluation of risk factors for CAD

Body mass index (BMI), systolic blood pressure (SBP), diastolic BP (DBP), serum levels of TG, HDL-C, LDL-C, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), smoking status, and medication use were collected as risk factors in all patients. BMI was calculated as weight (kg)/height (m)². The characteristics of patients were obtained from medical records

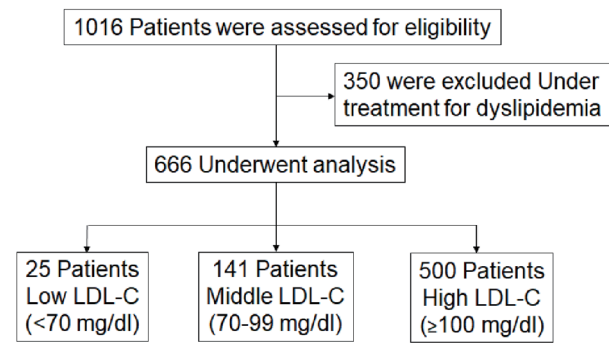


Figure 1. Flow chart of the enrollment process. LDL-C: low-density lipoprotein cholesterol.

with regard to history of HTN, DL and DM.

Medications

Information on medication use was obtained from medical records and included biguanide, dipeptidyl peptidase-4 inhibitor (DPP-4I), insulin, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor (ARB/ACEI), calcium channel blocker (CCB), β -blocker and diuretics.

Statistical analysis

A statistical analysis was performed using Excel 2016 (SSRI, Tokyo, Japan) and the Stat View statistical software package (Stat View 5; SAS Institute Inc., Cary, NC, USA). Continuous variables are shown as the mean \pm standard deviation. Categorical and continuous variables were analyzed for trends among the groups by the Cochran-Armitage trend test and Jonckheere-Terpstra trend test, respectively. A value of $P < 0.05$ was considered significant.

Results

Patient characteristics

One thousand sixteen patients were assessed for eligibility (Fig. 1). Three hundred fifty patients were excluded because they were receiving anti-lipidemic therapies. Six hundred sixty-six patients were divided into three groups: LDL-C < 70 mg/dL ($n = 25$, Low LDL-C group), 100 mg/dL $> LDL-C \geq 70$ mg/dL ($n = 141$, Middle LDL-C group) and $LDL-C \geq 100$ mg/dL ($n = 500$, High LDL-C group) (Table 1). The mean levels of LDL-C in the Low LDL-C, Middle LDL-C and High LDL-C groups were 57 mg/dL, 87 mg/dL and 133 mg/dL, respectively (P for trend < 0.001). In addition, the mean levels of TG in the Low LDL-C, Middle LDL-C and High LDL-C groups were 125 mg/dL, 132 mg/dL and 136 mg/dL, respectively (P for trend < 0.001). There were no significant differences in age, HDL-C, rate of HTN, HbA1c, FBS, SBP or medications (the

Table 1. Patients Characteristics in All Patients, Low LDL-C, Middle LDL-C and High LDL-C groups

	All patients (n = 666)	Low LDL-C (n = 25) (< 70 mg/dL)	Middle LDL-C (n = 141) (70 - 99 mg/dL)	High LDL-C (n = 500) (≥ 100 mg/dL)	P for trend
Age (yrs)	65 \pm 13	64 \pm 16	65 \pm 13	65 \pm 12	0.4
Male, n (%)	332 (50)	15 (60)	88 (62)	231 (46)	< 0.001
BMI, kg/m ²	24 \pm 4	23 \pm 4	23 \pm 3	24 \pm 4	0.01
Smoking, n (%)	226 (34)	10 (40)	56 (40)	160 (32)	0.03
DL, n (%)	208 (31)	6 (24)	26 (18)	176 (35)	< 0.001
TG, mg/dL	135 \pm 100	125 \pm 104	132 \pm 145	136 \pm 83	< 0.001
HDL-C, mg/dL	57 \pm 16	56 \pm 24	56 \pm 17	57 \pm 16	0.3
LDL-C, mg/dL	120 \pm 32	57 \pm 13	87 \pm 8	133 \pm 26	< 0.001
DM, n (%)	106 (16)	1 (4.0)	37 (26)	68 (14)	0.01
HbA1c, %	5.9 \pm 0.8	5.7 \pm 1.2	6.0 \pm 1.0	5.9 \pm 0.7	0.6
FBS, mg/dL	107 \pm 27	104 \pm 21	109 \pm 27	106 \pm 27	0.3
HTN, n (%)	386 (58)	15 (60)	86 (61)	285 (57)	0.2
SBP, mm Hg	135 \pm 20	127 \pm 20	134 \pm 19	136 \pm 20	0.1
DBP, mm Hg	78 \pm 14	71 \pm 15	77 \pm 14	79 \pm 13	0.02
Medications					
Biguanide, n (%)	31 (4.7)	0 (0)	8 (5.7)	23 (4.6)	0.5
DPP4-I, n (%)	49 (7.4)	1 (4.0)	15 (11)	33 (6.6)	0.1
Insulin, n (%)	10 (1.5)	1 (4.0)	6 (4.3)	3 (0.6)	< 0.001
ARB/ACEI, n (%)	191 (29)	7 (28)	50 (36)	134 (27)	0.04
CCB, n (%)	210 (32)	8 (32)	51 (36)	151 (30)	0.1
β -blocker, n (%)	47 (7.1)	2 (8.0)	7 (5.0)	38 (7.6)	0.2
Diuretics, n (%)	55 (8.3)	2 (8.0)	11 (7.8)	42 (8.4)	0.4

Continuous variables are expressed as mean \pm SD. BMI: body mass index; DL: dyslipidemia; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; DM: diabetes mellitus; HbA1c: hemoglobin A1c; FBS: fasting blood sugar; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; DPP4-I: dipeptidyl peptidase 4 inhibitor. ARB/ACEI: angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor; CCB: calcium channel blocker.

rates of biguanide, DPP4-I, CCB, β -blocker and diuretics). On the other hand, there were significant differences in the rates of males, smoking, DL, DM, insulin and ARB/ACEI, and BMI and DBP.

The prevalence of CAD, number of VD, Gensini score and CAC score

When $\geq 50\%$ of coronary stenosis was defined as significant stenosis, the prevalence of CAD values in the Low LDL-C, Middle LDL-C and High LDL-C groups were similar, at 52%, 47%, and 46%, respectively (P for trend 0.3) (Fig. 2a). The number of VD in the Low LDL-C, Middle LDL-C and High LDL-C groups was 0.8, 0.9 and 0.8, respectively (P for trend 1.0) (Fig. 2b). The Gensini score and CAC score were also similar between the groups (Fig. 2c, d). In addition, when $\geq 70\%$ of coronary stenosis was defined as significant stenosis, there were also no differences in %CAD and the number of

VD among Low, Middle and High LDL-C groups (Fig. 2e, f).

Discussion

In this study, we hypothesized that the target LDL-C level in patients for the primary prevention of CAD events should be < 70 mg/dL or < 100 mg/dL. We showed that LDL-C < 70 mg/dL or < 100 mg/dL under no anti-lipidemic therapies was not associated with the presence or severity of CAD. These results indicated that we need to screen with CCTA to prevent primary events regardless of LDL-C levels.

The most important finding in this study was that LDL-C < 70 mg/dL or < 100 mg/dL was not associated with lower the prevalence of CAD or a reduced severity of CAD, since there were no significant differences in the prevalence of CAD, number of VD, Gensini score or CAC score among the Low LDL-C, Middle LDL-C and High LDL-C groups. In a word, patients with lower LDL-C levels do not have a lower

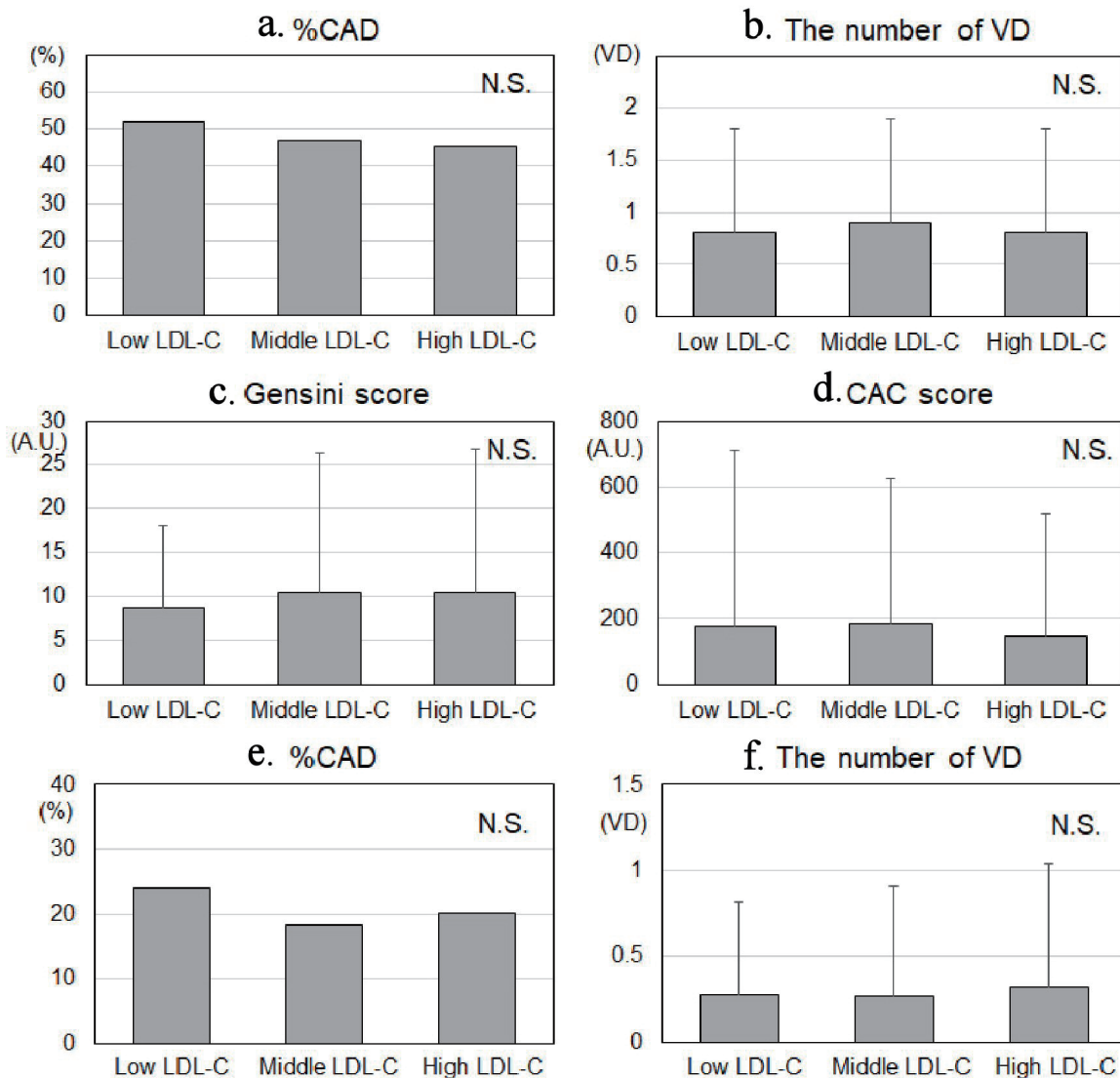


Figure 2. The prevalence of CAD (a, e), number of VD (b, f), Gensini score (c) and CAC score (d) in the Low LDL-C, Middle LDL-C and High LDL-C groups. The $\geq 50\%$ and $\geq 70\%$ of coronary stenosis were defined as significant stenosis in (a, b) and (e, f), respectively. CAD: coronary artery disease; number of VD: number of significantly stenosed coronary vessels; CACS: coronary artery calcium score; LDL-C: low-density lipoprotein cholesterol; N.S.: not significant; A.U.: arbitrary unit.

risk of CAD compared to patients with higher LDL-C (≥ 100 mg/dL). The High LDL-C group had lower rates of males, smoking and HTN compared to the Low and Middle LDL-C groups. Male, smoking and HTN are critical coronary risk factors [20]. Although there were no significant differences in HbA1c between the groups, the rate of insulin use in the High LDL-C group was lower than those in the Low and Middle LDL-C groups. The data indicated that the severity of DM in the High LDL-C group may be lower than those in the Low and Middle LDL-C groups. Although LDL-C levels in the High LDL-C group were relatively high (≥ 100 mg/dL), the rates of other risk factors were relatively low. Therefore, there were no significant differences in the presence or severity of CAD among the groups. In this study, patients who were clinically suspected of having CAD or who had at least one car-

diac risk factor underwent CCTA. Thus, even though patients may show low LDL-C levels under no treatment of DL, it may be advisable to aggressively perform CCTA when patients are clinically suspected of having CAD or coronary risk factors other than DL.

This study has several important limitations. First, this study was cross-sectional. Second, CCTA is not a gold standard for the evaluation of CAD, although recent studies have shown that its sensitivity and specificity were both approximately 95% of those for invasive coronary angiography for the identification of significant coronary stenosis [21]. A large-scale prospective study will be needed to address these issues.

In conclusion, the LDL-C level was not associated with atherosclerotic CAD, which indicates that we need to perform CCTA for screening to prevent primary cardiovascular events

even if patients without anti-lipidemic therapies show low levels of LDL-C.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consents were obtained.

Author Contributions

Conceptualization: Y. Katsuda and S.M. Validation: H.I., K.T., Y. Kawahira, and Y.I. Formal analysis: Y.S. and T.K. Investigation: M.S., H.N., and Y. Kawahira. Data curation: H.I., K.T., and Y.S. Writing-original draft: H.I., T.K., Y.S., and M.S. Writing-review and editing: S.M. Supervision: S.M.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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