Observational Study

Medicine

OPEN

The LDL-C/Apo B predicts coronary atherosclerotic heart disease in non-diabetic patients without high LDL-C

Hae Won Jung, MD[a], Moni Ra, MD[a], Han Joon Bae, MD[a], Seung-Pyo Hong, MD[a,*]

Abstract

The apolipoprotein B (Apo B), Apo B/A1 ratio, lipoprotein (a), and low-density lipoprotein cholesterol (LDL-C)/Apo B ratio are associated with coronary artery disease (CAD). However, the association between these parameters and CAD in non-diabetic patients without high LDL-C levels is unclear. Our goal was to assess which parameter was most strongly associated with CAD in non-diabetic patients without high LDL-C levels. This study included 487 non-diabetic patients with LDL-C < 130.0 mg/dL. All the patients underwent coronary computed tomographic angiography. We assessed the significance of each continuous atherogenic biomarker for CAD (incidence of coronary plaque and revascularization) without and after adjustment for standard risk factors. The LDL-C/Apo B ratio and lipoprotein (a) were significant risk factors for the incidence of coronary plaque on multivariate analysis after adjustment for standard risk factors. The LDL-C/Apo B ratio was significant for the incidence of revascularization in multivariate analysis after adjustment for standard risk factors. The degree of coronary calcification and plaque burden according to the tertile of LDL-C/Apo B showed significant differences between the groups. Our data indicate that LDL-C/Apo B ratio is the most predictive parameter for coronary atherosclerosis in non-diabetic patients without high LDL-C levels.

Abbreviations: Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, ASCVD = atherosclerotic cardiovascular disease, CAC = coronary artery calcification, CACS = coronary artery calcium score, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, HDL = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), sdLDL = small dense low-density lipoprotein, TC = total cholesterol.

Keywords: apolipoprotein a1, apolipoprotein b, coronary atherosclerosis, lipoprotein (a), low-density lipoprotein cholesterol

1. Introduction

High low-density lipoprotein cholesterol (LDL-C) level is a major risk factor for coronary artery disease (CAD). However, CAD also occurs in patients without high LDL-C levels. Sachdeva et al reported that approximately 75% of patients admitted to a hospital with a CAD event demonstrated a relatively normal LDL-C level of <130 mg/dL, and 23% had an LDL-C <70 mg/dL.[1] Diabetes is also a major risk factor for CAD.[2] To prevent CAD in non-diabetic patients without high LDL-C levels, it is necessary to identify CAD-causing lipoproteins other than LDL-C. The apolipoprotein B (Apo B), Apo B/A1 ratio, lipoprotein (a) (Lp [a]), and LDL-C/Apo B ratio have been useful in predicting atherosclerotic cardiovascular disease (ASCVD) and mortality.[3–10] However, it is unknown which lipid parameters are better predictors of CAD in non-diabetic patients without high LDL-C levels. According to the Adult Treatment Panel III, LDL-C ≥ 130.0 mg/dL was defined as a high level of LDL-C.[11] Therefore, we performed this study to assess which parameter was most strongly associated with CAD in non-diabetic patients with LDL-C < 130.0 mg/dL.

2. Methods

2.1. Study population and data collection

The study population was selected from the coronary computed tomographic angiography (CCTA) registry of the Daegu Catholic Medical Center (Daegu, Korea). Between January 2013 and September 2020, 3696 patients who visited our hospital for chest discomfort underwent CCTA and lipid profile evaluation (total cholesterol [TC], LDL-C, high-density lipoprotein cholesterol [HDL-C], triglyceride, apolipoprotein A1 [APO A1], APO B, and Lp [a]). Among the 3696 patients, we excluded 630 patients with a history of ASCVD and 1904 patients with LDL-C levels ≥ 130 mg/dL. Of the 1162 patients, 298 patients who underwent percutaneous coronary

HWJ and MR contributed equally to this work.

This work was supported by a research grant from Daegu Catholic University Medical Center.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Department of Cardiology, Daegu Catholic University Medical Center, Daegu, Republic of Korea.*

** Correspondence: Seung-Pyo Hong, Department of Cardiology, Daegu Catholic University Medical Center, 33 Duryugongwonro 17-gil, Nam-gu, Daegu 42472, Republic of Korea (e-mail: sphong@cu.ac.kr).*

How to cite this article: Jung HW, Ra M, Bae HJ, Hong S-P. The LDL-C/Apo B predicts coronary atherosclerotic heart disease in non-diabetic patients without high LDL-C. Medicine 2023;102:1(e32596).

Received: 14 October 2022 / Received in final form: 19 December 2022 / Accepted: 19 December 2022

http://dx.doi.org/10.1097/MD.0000000000032596

intervention or cardiac surgery, 217 who were maintained on lipid-lowering drugs, 135 with diabetes, 20 with end-stage renal disease, and 5 with motion artifacts on CCTA were excluded. Ultimately, 487 patients were included in the analysis. The inclusion and exclusion criteria are shown in the flow diagram (Fig. 1). The study protocol was approved by the institutional review board of Daegu Catholic University Medical Center. The institutional review board of Daegu Catholic University Medical Center waived the requirement for informed consent because of the retrospective nature of the study.

2.2. Acquisition and analysis of CCTA images

CT scans were performed using a 256-slice CT (Definition Flash; Siemens Healthineers AG) or a 512-slice CT (Revolution CT; GE Healthcare). All patients with an initial heart rate of ≥60 beats/minutes were administered an oral beta-blocker (propranolol 20 mg) to achieve a target heart rate of 50 to 60 beats/minutes. Sublingual nitroglycerin was administered immediately prior to scanning. An iodine contrast agent (60–70 mL) was administered into the antecubital vein within 10 seconds, followed by injection of 25 mL of saline solution injected at 5.0 mL/second. The CT-reconstructed imaging data were transferred to a GE Centricity system (GE Healthcare Bio-Sciences Corp.) for post-processing and subsequent image analysis. A radiologist independently read each scan at the central reading center. Atherosclerosis was defined as the presence of a coronary plaque. Plaques were defined as structures ≥ 1 mm^2 within and/or adjacent to the vessel lumen that were clearly distinguishable from the lumen and surrounding pericardial tissue.[12] Stenosis of 50% or more in 1 vessel was defined as 1 vessel disease, and stenosis of 50% or more in 2 or more vessels was defined as multivessel disease. Obstructive CAD was defined as at least 1 coronary artery with ≥50% stenosis.[13] The coronary artery calcium score (CACS) was acquired using the Agatston method with a commercially available reconstruction program for 3-dimensional reconstruction and measurement (Aquarius iNtuition TM Ver.4.4.12 TeraRecon).[14,15] CACS > 0 was defined as detectable coronary artery calcium.[16] After CCTA evaluation, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft [CABG]) was performed according to the discretion of the attending physician. The coronary revascularization rate was also investigated. All methods were performed in accordance with relevant guidelines and regulations.

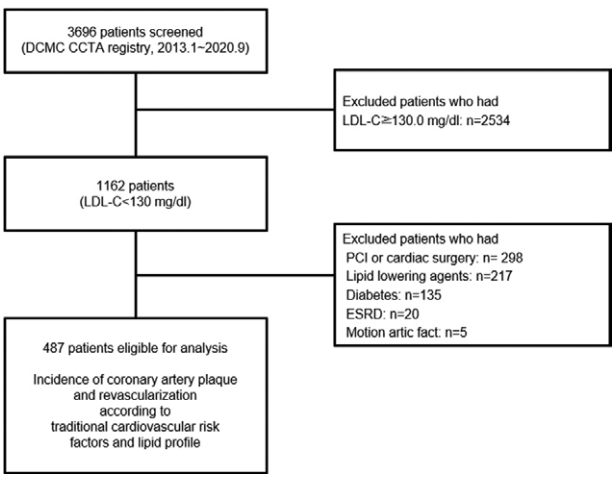

Figure 1. Enrollment flow chart for analysis. CCTA = coronary computed tomographic angiography, DCMC = Daegu catholic medical center, ESRD = end-stage renal disease, LDL-C = low-density lipoprotein cholesterol, PCI = percutaneous coronary intervention.

2.3. Statistics

Data are expressed as number (%) and mean ± standard deviation. Categorical data were compared using the chi-squared test or Fisher's exact test. Continuous variables were compared using the Student's *t* test and Kruskal–Wallis H test when they were normally and non-normally distributed, respectively. Unadjusted and adjusted logistic regression analyses were performed to identify potential independent predictors for the incidence of plaque and revascularization. These results are expressed as odds ratios. We assessed the significance of each specialized continuous atherogenic biomarker for CAD risk without adjustment and after adjustment for standard risk factors using 2 different models and multivariate analysis. Model 1 included age, sex, smoking, hypertension, and TC and HDL-C levels. Model 2 included age, sex, smoking, hypertension, TC, HDL-C and fasting blood glucose (FBG), estimated glomerular filtration rate (eGFR). Statistical significance was set at $P < .05$. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Base characteristics

Of the total 487 patients, the mean age was 53.8 ± 9.3 and the mean LDL-C was 93.7 ± 22.8 mg/dL. Coronary plaques were found in 268 patients (55.0%), and revascularization was performed in 50 patients (10.3%). The clinical characteristics of the patients, according to plaque type and revascularization, are shown in Table 1. In the plaque group compared to the no-plaque group, age and FBG were significantly higher, and eGFR and body mass index were significantly lower. The proportion of male, hypertension, and smokers was significantly higher in the plaque group than in the no plaque group. In the comparison of lipid profiles, the plaque group showed significantly lower HDL-C and LDL-C/Apo B ratios than the no plaque group. The Lp (a) level was significantly higher in the plaque group than in the no-plaque group. There were no significant differences in LDL-C and Apo B levels between the plaque and no-plaque groups. In the comparison between the no revascularization and revascularization groups, the revascularization group showed significantly higher age and FBG levels. The proportion of male and hypertension was significantly higher in the revascularization group than in the no-revascularization group. In the comparison of lipid profiles, the revascularization group showed significantly higher triglyceride, Apo B, and Apo B/A1 compared than the no revascularization group. The LDL-C/Apo B ratio was significantly lower in the revascularization group than in the no-revascularization group. There was no significant difference in LDL-C levels between the revascularization and no revascularization groups.

3.2. Logistic regression analysis for the incidence of plaque

Univariate analysis without adjustment demonstrated that Lp (a) and LDL-C/Apo B were significantly associated with plaque incidence. After multivariate adjustment for the parameters in Model 1, LDL-C/Apo B and Lp (a) levels were significant. In the fully adjusted model (model 2), which included FBG and eGFR, Lp (a) and LDL-C/Apo B levels remained significant ($P < .05$). The C statistic for model 2 alone was 0.811 and increased to 0.818 when Lp (a) was added, and increased to 0.818 when LDL-C/apo B was added to model 2 (Table 2).

3.3. Logistic regression analysis for the incidence of revascularization

Univariate analysis without adjustment demonstrated that Apo B, Apo B/A1, and LDL-C/Apo B were significantly associated with the incidence of revascularization. After multivariate adjustment for the parameters in model 1, only LDL-C/Apo B

was significant. In the fully adjusted model (model 2), which included FBG and eGFR, LDL-C/Apo B ratio remained significant ($P < .05$). The C statistic for model 2 alone was 0.755, which increased to 0.792 when LDL-C/Apo B was added to model 2 (Table 3).

3.4. Characteristics according to tertiles of the LDL-C/Apo B ratio

The clinical characteristics of the patients stratified by tertiles of LDL-C/Apo B ratio are shown in Table 4. The cutoff points between tertiles were 1.053 (between the first and second tertiles) and 1.186 (between the second and third tertiles). In terms of CCTA characteristics, the proportion of patients with CACS > 0, plaque, and obstructive CAD significantly increased in the order of tertiles 3, 2, and 1.

4. Discussion

The primary findings of our study are as follows: the LDL-C/Apo B ratio and Lp (a) predict the incidence of plaque in non-diabetic patients without high LDL-C levels. The LDL-C/Apo B ratio predicts the incidence of revascularization after CCTA in non-diabetic patients without high LDL-C levels. Coronary artery calcification and plaque burden increased significantly as the LDL-C/Apo B ratio decreased.

This study was conducted in patients with no history of ASCVD, no diabetes, and an LDL-C level of 130 or less. According to the 2018 Korean dyslipidemia management guidelines, patients who meet the above criteria are not recommended for statin use in the low-to moderate-risk group.[17] However, in clinical practice, ASCVD occurs in these patients, and 10.3% of the patients in this study underwent revascularization after CCTA evaluation. Currently, lowering LDL-C is the main treatment target for preventing ASCVD.[17,18] However, biomarkers

Table 1

Characteristics of individuals according to presence of plaque.

Variables	No plaque (n = 219)	Plaque (n = 268)	*P* value	No revascularization (n = 437)	Revascularization (n = 50)	*P* value
Clinical characteristics						
Age, yr	49.5 ± 10.6	57.4 ± 6.1	<.001	53.3 ± 9.4	58.5 ± 6.7	<.001
Male	93 (42.5)	200 (74.6)	<.001	254 (58.1)	39 (78.0)	.007
Hypertension	55 (25.1)	112 (41.8)	<.001	141 (32.3)	26 (52.0)	.005
Smoker	55 (25.1)	106 (39.6)	.001	139 (31.8)	22 (44.0)	.083
SBP (mm Hg)	124.9 ± 18.4	125.6 ± 16.8	.648	125.4 ± 17.4	124.1 ± 18.5	.625
DBP (mm Hg)	75.4 ± 13.3	75.6 ± 10.8	.809	75.6 ± 12.0	75.2 ± 11.8	.840
BMI (kg/m^2)	24.9 ± 4.4	24.1 ± 3.0	.014	24.5 ± 3.8	24.0 ± 3.1	.361
eGFR (mL/min/1.73 m^2)	99.7 ± 16.6	93.2 ± 14.3	<.001	96.6 ± 15.8	92.0 ± 14.5	.054
EF (%)	56.7 ± 12.0	56.8 ± 12.4	.945	57.0 ± 11.9	54.5 ± 14.0	.171
FBG (mg/dL)	99.6 ± 18.9	104.2 ± 23.4	.019	101.5 ± 20.4	108.0 ± 29.7	.044
Lipid profile						
TC (mg/dL)	155.4 ± 26.2	152.3 ± 27.7	.226	153.2 ± 26.2	158.1 ± 33.3	.239
TG (mg/dL)	109.3 ± 87.2	121.8 ± 89.1	.127	111.0 ± 81.4	161.5 ± 127.3	<.001
HDL-C (mg/dL)	50.0 ± 15.8	46.7 ± 14.2	.016	48.6 ± 15.1	44.9 ± 13.8	.100
LDL-C (mg/dL)	94.6 ± 21.5	92.9 ± 23.7	.435	93.5 ± 22.4	95.6 ± 26.1	.532
Lp (a) (mg/dL)	18.2 ± 19.3	22.6 ± 26.5	.040	20.1 ± 23.1	25.5 ± 27.5	.128
Apo B (mg/dL)	83.4 ± 17.3	85.3 ± 19.2	.255	83.7 ± 17.6	90.4 ± 23.2	.015
Apo A1 (mg/dL)	132.6 ± 28.8	129.2 ± 30.8	.205	131.0 ± 29.3	128.9 ± 34.9	.646
Apo B/ A1	0.662 ± 0.213	0.705 ± 0.259	.051	0.677 ± 0.229	0.761 ± 0.313	.019
LDL-C/Apo B	1.14 ± 0.171	1.09 ± 0.156	.001	1.112 ± 0.163	1.056 ± 0.168	.012

Data are given as mean ± SD, or as number (%).

Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, BMI = body mass index, EF = ejection fraction, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), TC = total cholesterol, TG = triglyceride.

Table 2

Association of incidence of coronary plaque with atherogenic lipoprotein parameters as continuous variables.

Variable	Odd ratio (95% CI)	*P* value	*C* Statistic
Apo B	1.006 (0.996–1.016)*	.255	0.530
Model 1	1.020 (0.998–1.043)	.079	0.815
Model 2	1.016 (0.992–1.039)	.194	0.812
Apo B/A1 ratio	2.14 (0.993–4.60)*	.052	0.542
Model 1	2.74 (0.679–11.15)	.159	0.813
Model 2	2.86 (0.677–12.05)	.153	0.812
Lp (a)	1.008 (1.000–1.016)*	.042	0.528
Model 1	1.012 (1.001–1.023)	.026	0.819
Model 2	1.013 (1.002–1.025)	.025	0.818
LDL-C/Apo B	0.155 (0.049–0.493)*	.002	0.597
Model 1	0.101 (0.022–0.457)	.003	0.819
Model 2	0.099 (0.019–0.504)	.005	0.818

Odd ratio (95% CI) is expressed as the risk for the 75th percentile versus the 25th percentile. Model 1 was adjusted by age, sex, smoking, hypertension, TC and HDL-C. Model 2 was model 1 plus eGFR and FBG (C statistic, 0.811).

Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, eGFR = estimated glomerular filtration, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), TC = Total cholesterol.

*Variable is unadjusted for any other risk factors.

that show better predictive performance for ASCVD than for LDL-C have been reported. Apo B is a key structural protein component of all major atherosclerotic lipoproteins (LDL-C, VLDL-C, IDL-C, and Lp [a]).[3] It has been shown to be a better predictor of ASCVD than LDL-C.[19,20] The Apo B/A1 ratio is also a good predictor of ASCVD. The Apo A1 is an anti-atherosclerotic lipoprotein and the main apolipoprotein incorporated into HDL-C. Therefore, the Apo B/A1 ratio represents the cholesterol balance between atherogenic and anti-atherogenic lipoprotein particles.[3] Several prospective studies, including the INTERHEART and AMORIS studies, have demonstrated a positive association between ASCVD and the Apo B/A1 ratio.[5,6] Lp (a) is a low-density lipoprotein-like particle and apolipoprotein(a) attached to apolipoprotein B via a disulfide bridge. Observational and genetic evidence strongly supports a causal relationship between high Lp (a) levels and an increased risk of ASCVD.[21] However, Afshar et al demonstrated that cardiovascular risk associations with Lp (a) are attenuated in patients with LDL-C ≤ 135 mg/dL (3.5 mmol/L).[7] In addition, in this study, Lp (a) was an independent predictor of plaque formation, but not revascularization.

Several studies have reported that small dense low-density lipoprotein (sdLDL) levels increase the risk of ASCVD.[22–24] Ikezaki et al demonstrated that sdLDL is the most atherogenic lipoprotein parameter compared to other lipoprotein parameters, including low-density lipoprotein triglycerides, triglyceride-rich lipoprotein cholesterol, remnant lipoprotein particle cholesterol, direct LDL-C, Lp (a), large buoyant LDL-C, and VLDL-C.[24] The increased atherogenesis of sdLDL is associated with the specific biochemical properties of these particles. The small size makes penetration into the arterial wall easier, and smaller LDL particles have a decreased receptor-mediated uptake. Therefore, the half-life of sdLDL is longer than that of the large LDL particles. A longer circulation time increases the possibility of atherogenic modification of sdLDL in the blood.[25] The LDL-C/Apo B ratio has been identified as a marker of small dense low-density lipoprotein (sdLDL). Hirano et al found that an LDL-C/Apo B ratio of 1.2 corresponds to an LDL diameter of 25.5 nm, has been proposed as a cutoff value between sdLDL and large buoyant LDL.[26] A low LDL-C/Apo B ratio has been associated with increased ASCVD risk.[9,10] The present study demonstrated that the LDL-C/Apo B ratio was an independent predictor of both plaque and revascularization, and the proportion of patients with coronary artery calcification (CAC) exceeding 0, plaque, and obstructive CAD increased significantly as the LDL-C/Apo B ratio decreased. These results suggest that sdLDL affects not only the occurrence of plaque but also its severity, which is consistent with the findings of Koba et al.[27] This study demonstrated the role of sdLDL in coronary atherosclerosis in patients with LDL-C < 130.0 mg/dL. Kim et al compared CAC progression based on the Apo B/LDL-C ratio. In their study, the High Apo B (Apo B > 102 mg/dL)/Low LDL-C (LDL-C < 131 mg/dL) group showed a significantly higher risk of CAC progression than the low Apo B/low LDL-C group.[28] These results suggest that the effect of sdLDL on coronary atherosclerosis is significant, even in patients with low LDL-C levels. Previous studies have revealed that ASCVD risk associations with Lp (a) are attenuated in patients with low LDL-C.[7,29] Thus, different types of

Table 3

Association of incidence of revascularization with atherogenic lipoprotein parameters as continuous variables.

Variable	Odd ratio (95% CI)	*P* value	*C* Statistic
Apo B	1.021 (1.004–1.038)*	.015	0.592
Model 1	1.011 (0.981–1.042)	.472	0.772
Model 2	1.005 (0.974–1.037)	.777	0.775
Apo B/A1 ratio	3.69 (1.22–11.13)*	.021	0.574
Model 1	1.60 (0.255–10.07)	.615	0.770
Model 2	1.340 (0.207–8.681)	.759	0.776
Lp (a)	1.008 (0.998–1.019)*	.131	0.564
Model 1	1.007 (0.996–1.019)	.215	0.771
Model 2	1.009 (0.997–1.021)	.145	0.781
LDL-C/Apo B	0.120 (0.022–0.645)*	.013	0.603
Model 1	0.061 (0.008–0.478)	.008	0.791
Model 2	0.085 (0.010–0.727)	.024	0.792

Odd ratio (95% CI) is expressed as the risk for the 75th percentile versus the 25th percentile. Model 1 was adjusted by age, sex, smoking, hypertension, TC and HDL-C. Model 2 was model 1 plus eGFR and FBG (C statistic, 0.755) Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, eGFR = estimated glomerular filtration, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), TC = Total cholesterol.

*Variable is unadjusted for any other risk factors.

Table 4

Characteristics of individuals stratified by tertiles of the LDL-C/ Apo B ratio.

Variables	Total patients (n = 487)	Tertile 1 of the LDL-C/ Apo B ≤ 1.053 (n = 162)	Tertile 2 of the LDL-C/ Apo B 1.053–1.186 (n = 163)	Tertile 3 of the LDL-C/ Apo B > 1.186 (n = 162)	*P* value
CACS	126.9 ± 406.7	149.8 ± 340.8	131.9 ± 497.5	99.1 ± 364.5	.524
CAC > 0	209 (42.9)	88 (54.3)	66 (40.5)	55 (34.0)	.001
CAC > 400	44 (9.0)	19 (11.7)	13 (8.0)	12 (7.4)	.337
Plaque	268 (55.0)	109 (67.3)	87 (53.4)	72 (44.4)	<.001
Obstructive CAD	112 (23.0)	48 (29.6)	33 (20.2)	31 (19.1)	.048
Multivessel disease	29 (6.0)	13 (8.0)	8 (4.9)	8 (4.9)	.395
Revascularization	50 (10.3)	23 (14.2)	15 (9.2)	12 (7.4)	.113

Data are given as mean ± SD, or as number (%).

Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, BMI = body mass index, CAC = coronary artery calcification, CACS = coronary artery calcium score, CAD = coronary artery disease, CCTA = coronary computed tomographic angiography, EF = ejection fraction, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), TC = total cholesterol, TG = triglyceride.

atherogenic lipoprotein parameters may better represent residual cardiovascular risk, depending on the patient's LDL-C level.

This study has several strengths. First, this study is the first to compare the effects of Apo B, Apo B/Apo A1, Lp (a), and LDL-C/Apo B on coronary atherosclerosis in low-risk patients who do not recommend statin therapy. Second, unlike previous studies that reported the relationship between the LDL-C/Apo B ratio and cardiovascular events,[9,10] our study reported the relationship between the LDL-C/Apo B ratio and coronary atherosclerosis on CCTA. Therefore, we investigated the role of LDL-C/Apo B ratio in the early stages of atherosclerosis. However, this study had several limitations. First, it was a single-center study. Second, the study population was comprised of Koreans; studies with other races are necessary to confirm and generalize our findings. Third, because our study targeted patients who underwent CCTA for chest discomfort, the incidence of plaque formation was high. Therefore, to apply the results of this study to the general population, a large-scale study that includes asymptomatic patients should be conducted.

5. Conclusion

Our data indicated that the LDL-C/Apo B ratio is the most predictive parameter for coronary atherosclerosis and its severity in non-diabetic patients without high LDL-C levels.

Author contributions

Conceptualization: Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Data curation: Hae Won Jung, Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Formal analysis: Hae Won Jung, Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Funding acquisition: Hae Won Jung, Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Investigation: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Methodology: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Project administration: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Resources: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Software: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Supervision: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Validation: Hae Won Jung, Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Visualization: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.
Writing – original draft: Hae Won Jung, Moni Ra, Han Joon Bae, Seung-Pyo Hong.
Writing – review & editing: Hae Won Jung, Han Joon Bae, Seung-Pyo Hong.

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