Cardiovascular Revascularization Medicine 61 (2024) 85–92

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

journal homepage: www.sciencedirect.com/journal/cardiovascular-revascularization-medicine

Prognostic role of apolipoproteins on long-term major adverse cardiac events after percutaneous coronary intervention

Hiroshi Kawahara [a,*], Akihiro Endo [a], Kazuhiko Uchida [b], Kazuaki Tanabe [a]

[a] Division of Cardiology, Shimane University Faculty of Medicine, Japan
[b] Division of Cardiology, Masuda Red Cross Hospital, Japan

ARTICLE INFO

Keywords:
Low-density lipoprotein cholesterol
High-density lipoprotein cholesterol
Apolipoprotein B
Apolipoprotein A1
Long-term major adverse cardiac events
Percutaneous coronary intervention

ABSTRACT

Background/Purpose: Apolipoprotein (apo) levels are associated with coronary risk. However, the relationship between apo levels after percutaneous coronary intervention (PCI) and long-term major adverse cardiac events (MACEs) remains unclear. We aimed to investigate the association between lipid levels, including apo, at follow-up, and long-term MACEs in patients undergoing PCI.

Methods/Materials: In total, 241 patients who underwent PCI between January 2004 and August 2008 were included in this study. MACEs were defined as cardiac death, acute coronary syndrome, or coronary revascularization of new lesions. The primary endpoint was MACE, and the secondary endpoint was a composite of cardiac death and acute coronary syndrome.

Results: During a mean follow-up period of 2079 days, the following cardiovascular events occurred in 78 patients: cardiovascular death ($n = 1$), non-fatal acute myocardial infarctions ($n = 10$), and revascularizations of new lesions ($n = 67$). Multivariate cox's proportional hazards analysis showed that the apo B level was an independent risk factor for MACEs (hazard ratio 1.11, 95 % confidence interval 1.03–1.20; $P = 0.009$). In the Kaplan–Meier estimation for primary endpoints, significant differences were observed in the apo B level and apo B/apo A1 ratio ($P = 0.04$ and $P = 0.004$, respectively). However, there was no difference in the LDL-C level and LDL-C/HDL-C ratio. At the secondary endpoint, only the apo B/apo A1 ratio was a prognostic factor ($P = 0.007$).

Conclusions: In the long-term cardiovascular events of patients undergoing PCI, the apo B level and apo B/apo A1 ratio were more valuable prognostic factors for cardiovascular events compared to the LDL-C level and LDL-C/HDL-C ratio.

1. Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) levels are associated with atherosclerotic cardiovascular disease (ASCVD) [1]. Statin therapy is a well-established approach for the secondary prevention of ASCVD and it has been reported to reduce the risk of cardiovascular events by 21 % for every 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C [2]. However, statin therapy cannot completely prevent cardiovascular events after percutaneous coronary intervention (PCI). Apolipoprotein B (apo B) and apo A1 levels and the apo B/apo A1 ratio are markers for coronary risk even in patients receiving lipid-lowering therapy [3]. In particular, apo B is strongly correlated with non-high-density lipoprotein cholesterol (HDL-C) [4]. A meta-analysis of combined primary and secondary prevention reported that lowering apo B levels with statins reduces the risk of cardiovascular events, independent of the reduction in LDL-C levels [5]. However, the relationship between apo levels and ASCVD among patients undergoing PCI remains unclear. The B/apo A1 ratio during follow-up has been reported to have better predictive accuracy than the total cholesterol (T-Cho)/HDL-C ratio or lipoprotein (a) in the mid-term clinical outcomes of patients with LDL-C levels < 70 mg/dL after PCI [6].

Therefore, this study aimed to investigate whether apo levels are more closely associated with long-term major adverse cardiac events (MACEs) than conventional lipid levels in patients undergoing PCI.

2. Materials and methods

2.1. Study population and study design

This was a single-center, prospective, observational study. It used the clinical records of patients who underwent PCI between January 2004 and August 2008 at Masuda Red Cross Hospital. If the patient had undergone more than one PCI during the study period, the first PCI was considered as index PCI. Considering the potential for post-PCI changes in pharmacotherapy, we employed data from follow-up CAG or occurrences

* Corresponding author at: Division of Cardiology, Shimane University Faculty of Medicine, 89–1 Enya-cho, Izumo 693–8501, Japan.
E-mail address: k-hiroshi@hb.tp1.jp (H. Kawahara).

http://dx.doi.org/10.1016/j.carrev.2023.10.012
Received 17 August 2023; Received in revised form 14 October 2023; Accepted 17 October 2023
Available online 21 October 2023

of MACE for this study. We excluded patients; 1) who did not have all background data available, 2) who could not be followed for at least 5 years in spite of no events having occurred, 3) who had no follow-up coronary angiography (CAG), 4) who were scheduled for cardiac surgery, and 5) who did not consent to this study. The primary endpoint was MACE, which was defined as cardiac death, acute coronary syndrome (acute myocardial infarction (AMI) and unstable angina), or coronary revascularization for new lesions. Scheduled PCI at the time of enrolment was not considered as a MACE. Target lesion revascularization for stable angina was also not included. The secondary endpoint was composite of cardiac death and acute coronary syndrome. The association between these endpoints and standard lipid variables and apos was investigated. Medical condition data from patients who did not visit our hospital were collected by letter or phone.

Data for age, gender, height, weight, body mass index (BMI), smoking habits, risk factors for coronary artery disease, laboratory parameters, and cardiovascular medications at the time of follow-up CAG or MACE were obtained by checking hospital records. BMI was calculated as the ratio between weight and height squared (in kg/m^2). Laboratory parameters, included T-Cho, HDL-C, LDL-C, triglyceride (TG), apo A1, apo B, estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c), were collected on admission. Non-HDL-C was the difference between HDL-C and T-Cho. We calculated the ratio of apo B/apo A-1, LDL-C/HDL-C, and LDL/apo B. The ethics committee of Masuda Red Cross Hospital approved this study (No. 39), which was conducted in accordance with the directives of the Helsinki Declaration. All patients provided informed consent before participation in this study.

2.2. Laboratory measurements

T-Cho was measured by enzymatic method using T-CHO-S KL (SYSMEX, Hyogo, JAPAN). LDL-C was measured by direct method using Determiner L LDL-C (KYOWA MEDEX, Tokyo, JAPAN) and HDL-C was measured by absorbance measurement using Determiner L HDL-C (KYOWA MEDEX, Tokyo, Japan). TG was measured by absorbance measurement using L-Type TG M (Wako Pure Chemical Industries, Osaka, JAPAN). Apo A1 and apo B were measured by immunonephelometry using TAC-3 test (MEDICAL & BIOLOGICAL LABORATORIES, Tokyo, JAPAN).

2.3. Risk factor

As risk factors for cardiovascular disease, HbA1c (according to the National Glycohemoglobin Standardization Program) [7], dyslipidemia, hypertension, eGFR, and current smoking status were examined. Dyslipidemia was defined as LDL-C level ≥ 140 mg/dL, HDL-C level < 40 mg/dL, TG level ≥ 150 mg/dL, and/or if the patient used lipid-lowering drugs. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or if the patient used antihypertensive drugs.

2.4. Statistical analysis

All analyses were performed using SPSS version 26 software program (SPSS Inc., Chicago, IL, USA). Participants who experienced a MACE were censored on the day of the MACE, and all others were censored on the day of the last visit, the date indicated in the answer letter, or the date confirmed by telephone. The groups with MACE and without MACE were compared using the Chi-square test or the Fisher's exact-test for categorical variables and the Mann–Whitney *U* test, the two-sample *t*-test or the Welch test for continuous variables. The normal distribution of the continuous variables was confirmed using the Shapiro–Wilk test. The continuous variables with normal distribution were tested for homoscedasticity with the Levene test and were analyzed using the two-sample *t*-test or Welch test. If the normal distribution test failed, they were compared using the Mann–Whitney test. Continuous variables are presented as medians and quartiles.

The hazard ratio (HR) and 95 % confidence intervals (CI) assessing the risk of MACE were estimated using univariate and multivariate analyses with the Cox proportional hazard model. Multivariate analysis was performed in two ways: with only the prevailing variables in the univariate analysis, and with the addition of variables related to cardiovascular events. To assess the effects of apo B and apo B/apo A1 ratio, patients were divided into two groups based on the median value and Kaplan–Meier estimation was performed. LDL-C and LDL-C/HDL-C ratio were evaluated in the same way for comparison. The median value case was assigned to the lower group in all situations. Kaplan–Meier event free curves were compared using the log-rank test. In all analyses, statistical significance was set at a P value of <0.05.

3. Results

Study flow is shown in Fig. 1. During the follow-up period of the study, 458 patients underwent PCI, and 217 patients were excluded owing to lack of follow-up CAG, incomplete data, or lack of follow-up for at least 5 years if no MACE occurred. Twenty-five patients were not eligible because of the following reasons: 13 passed away on admission for initial PCI (12 had AMI, 1 had pneumonia after stable angina), 8 were distant residents, and 4 were scheduled for cardiac surgery after initial PCI (3 had coronary artery bypass grafting (CABG), 1 had valvular disease). The remaining 192 patients were not included for the following reasons: 106 had incomplete apo or other data, 38 had no follow-up CAG because of advanced age or renal dysfunction, 28 had no data because of noncardiovascular death before follow-up CAG or MACE, 16 had unknown outcome within 5 years, 1 was suspected of AMI with CAG declined, 1 was recommended for CABG with refusal, and 2 had other reasons. As a result, we analyzed 241 patients in this study. The reasons for index PCI were as follows: 72 cases of acute myocardial infarction, 25 cases of unstable angina, and 144 cases of stable angina. Patient characteristics are shown in Table 1. The average follow-up is 2079 days from the date of index PCI. MACE occurred in 78 patients: 1 cardiac death, 10 non-fatal AMI, and 67 coronary revascularizations for new lesions, including 8 patients with unstable angina. Due to the occurrence of MACE before the follow-up CAG, laboratory parameters were assessed at the time of admission when MACE occurred, which included 1 cardiac death, 1 non-fatal AMI, and 3 unstable angina cases. There were significant differences in age (P = 0.009), female sex (P = 0.009), height (P = 0.03), weight (P = 0.04), follow-up period (P < 0.001), HDL-C (P = 0.02), apo B (P = 0.005), apo B/A1 ratio (P = 0.003), LDL-C/HDL-C ratio (P = 0.005), and non-HDL-C (P = 0.02) between patients with and without MACE.

3.1. Primary endpoint

For the primary endpoint, age (P = 0.03), female sex (P = 0.02), HDL-C (P = 0.04), apo B (P = 0.006), apo B/apo A1 ratio (P = 0.02), and non-HDL-C (P = 0.03) were detected as predictors of long-term MACE after PCI in Cox proportional hazard models with univariate analysis (Table 2). Multivariate analysis with the addition of variables related to cardiovascular events showed that apo B was an independent prognostic factor (HR: 1.11, 95 % CI: 1.03 to 1.20; P = 0.009). In the multivariate analysis utilizing only the significant factors from the univariate analysis, apo B remained the sole significant factor.

The Kaplan–Meier estimation with log-rank test showed that there was a significant difference in the incidence of MACEs between the two groups for apo B and apo B/apo A1 ratio (P = 0.04 and P = 0.004, respectively), whereas no significant difference was found for LDL-C and LDL-C/HDL-C ratio (P = 0.07 and P = 0.08, respectively) (Fig. 2).

3.2. Secondary endpoint

In terms of secondary endpoints, the Cox proportional hazard models using univariate analysis revealed statistical disparities in HbA1c (P = 0.03), hypertension (P = 0.02), antiplatelet therapy (P = 0.01), and the

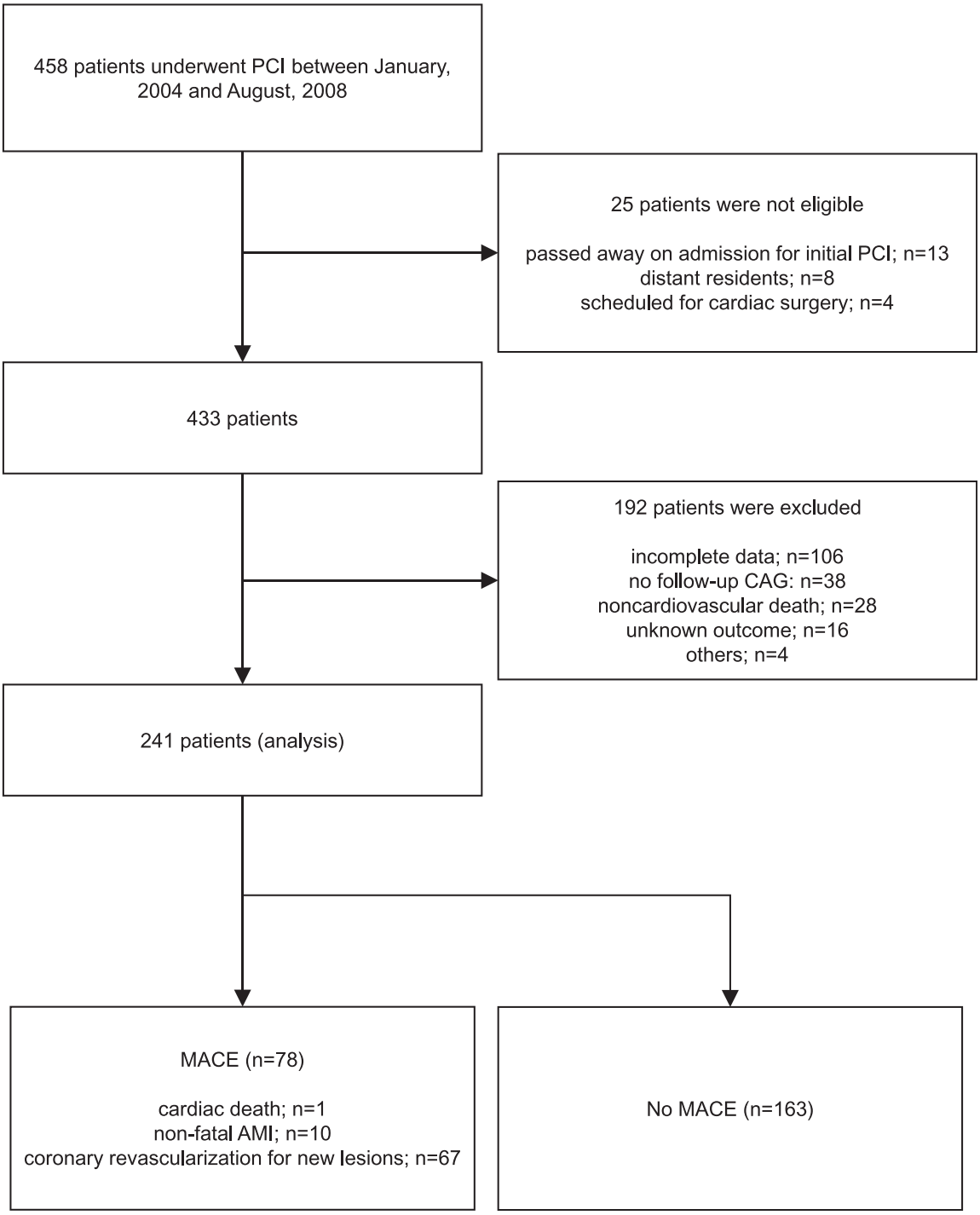

Fig. 1. Study population and enrolment process. AMI; acute myocardial infarction, MACE; major adverse cardiac event, PCI; percutaneous coronary intervention.

apo B/apo A1 ratio (P = 0.02). The significant results of multivariate analysis were hypertension (HR: 0.27, 95 % CI: 0.09 to 0.81; P = 0.02), antiplatelet therapy (HR: 0.02, 95 % CI: 0.002 to 0.16; $P < 0.001$), and apo B/apo A1 ratio (HR: 13.66, 95 % CI: 1.38 to 134.87; $P = 0.03$). Although the difference between the two groups disappeared for apo B ($P = 0.206$), the event rate was higher in the high apo B/apo A1 ratio group ($P = 0.007$) in the Kaplan–Meier estimation with log-rank test. LDL-C and LDL-C/HDL-C ratio remained not significantly different ($P = 0.170$, $P = 0.091$, respectively) (Fig. 3).

4. Discussion

This study found that long-term recurrence of cardiovascular events after PCI was closely associated with apo B and apo B/apo A1 ratio rather than with LDL-C and LDL-C/HDL-C ratio. In post-PCI patients, the apo B/apo A1 ratio was shown to be a better prognostic factor than the T-Cho/HDL-C ratio and lipoprotein (a) only in the mid-term follow-up of patients achieving LDL levels < 70 mg/dL [6]. We found an association between cardiovascular events and apos in this study, without limiting the patients with

Table 1
Demographic and clinical characteristics of the patients.

	With MACE (n = 78)	Without MACE (n = 163)	P value
Age	68.0 (59.8, 74.0)	72.0 (65.0, 78.0)	0.009
Female	14 (18)	56 (34)	0.009
Height (cm)	161.1 (154.9, 166.0)	158.0 (150.0, 164.0)	0.03
Weight (kg)	61.0 (54.3, 67.0)	57.0 (50.0, 66.0)	0.04
BMI (kg/m^2)	24.1 (22.1, 26.0)	23.3 (21.2, 25.2)	0.18
Follow-up period (day)	1003 (396, 1729)	2655 (2010, 3198)	<0.001
Current smoke	14 (18)	24 (15)	0.52
eGFR (mL/min/1.73 m^2)	65.7 (56.1, 76.3)	65.7 (55.6, 80.1)	0.91
HbA1c(NGSP) (%)	5.8 (5.4, 6.6)	5.7 (5.3, 6.5)	0.17
DL	36 (46)	73 (45)	0.84
HT	40 (51)	92 (56)	0.45
Medication			
Statin	32 (41)	66 (40)	0.94
RAAS inhibitor	43 (55)	84 (52)	0.60
β-blocker	8 (10)	31 (19)	0.08
Ca-blocker	40 (51)	69 (42)	0.19
Antiplatelet therapy	77 (99)	162 (99)	0.54
T-Cho (mg/dL)	184.5 (163.3, 203.3)	181.0 (159.0, 198.0)	0.34
HDL-C (mg/dL)	48.5 (42.0, 57.0)	53.0 (44.0, 68.0)	0.02
LDL-C (mg/dL)	112.0 (96.5, 128.0)	105.0 (89.0, 120.0)	0.08
TG (mg/dL)	126.5 (92.0, 175.0)	113.0 (81.0, 155.0)	0.05
Apo A1 (mg/dL)	134.0 (121.0, 155.0)	140.0 (124.0, 159.0)	0.13
Apo B (mg/dL)	88.0 (77.8, 103.0)	82.0 (70.0, 92.0)	0.005
Apo B/apo A1 ratio	0.66 (0.55, 0.77)	0.58 (0.48, 0.70)	0.003
LDL-C/HDL-C ratio	2.29 (1.76, 2.78)	2.00 (1.51, 2.48)	0.005
Non-HDL-C (mg/dL)	134.5 (115.3, 153.3)	123.0 (104.0, 142.0)	0.02

The data are shown as median (interquartile range; 25th, 75th%) or no. (%). BMI and non-HDL are calculated by dividing body weight by the square of height and subtracting LDL from T-Cho, respectively.
Apo, apolipoprotein; BMI, body mass index; DL, dyslipidemia; eGFR; estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; RAAS, renin angiotensin aldosterone system; T-Cho, total cholesterol; TG, triglyceride.

Table 2
Univariate and multivariate Cox's proportional hazards analysis.

	Univariate		Multivariate	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age	0.98 (0.96–1.00)	0.03	0.98 (0.96–1.01)	0.14
Female	0.50 (0.28–0.90)	0.02	0.58 (0.31–1.09)	0.89
Height	1.02 (1.00–1.05)	0.10		
Weight	1.01 (1.00–1.03)	0.15		
BMI	1.02 (0.96–1.09)	0.51		
Current smoke	1.18 (0.66–2.10)	0.58		
eGFR	1.00 (0.99–1.01)	0.94		
HbA1c(NGSP)	1.17 (0.94–1.46)	0.15		
DL	0.95 (0.61–1.48)	0.81		
HT	0.87 (0.56–1.36)	0.54		
Medication				
Statin	0.96 (0.61–1.51)	0.87		
RAAS inhibitor	1.14 (0.73–1.78)	0.58		
β-blocker	0.56 (0.27–1.16)	0.12		
Ca-blocker	1.36 (0.87–2.12)	0.17		
Antiplatelet therapy	0.40 (0.06–2.88)	0.36		
T-Cho	1.00 (1.00–1.01)	0.31		
HDL-C	0.98 (0.97–1.00)	0.04	1.01 (0.96–1.05)	0.80
LDL-C	1.01 (1.00–1.02)	0.13	0.99 (0.97–1.01)	0.43
TG	1.00 (1.00–1.00)	0.17		
Apo A1	1.00 (0.99–1.00)	0.26	0.96 (0.92–1.01)	0.08
Apo B	1.02 (1.01–1.03)	0.006	1.11 (1.03–1.20)	0.009
Apo B/apo A1 ratio	3.82 (1.30–11.27)	0.02	0.001 (0.00–1.21)	0.06
LDL-C/HDL-C ratio	1.28 (1.00–1.63)	0.05		
Non-HDL-C	1.01 (1.00–1.02)	0.03	0.99 (0.97–1.01)	0.34

The data are shown as HR (95 % CI). Calculation of BMI and non-HDL is identical to that in Table 1. The significant factor of multivariate analysis was only apo B whether using only significant factors in the univariate analysis or including general risk factors.
Apo, apolipoprotein; BMI, body mass index; CI, confidence interval; DL, dyslipidemia; eGFR; estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; RAAS, renin angiotensin aldosterone system; T-Cho, total cholesterol; TG, triglyceride.

LDL-C levels < 70 mg/dL and in the long-term, instead of in the mid-term after PCI. It is also important to note that all patients in this study had cardiac catheterization, except for those with sudden cardiac death, ensuring accurate identification of coronary artery lesions.

High LDL-C levels are epidemiologically associated with ASCVD [8], and a Mendelian randomized study also showed that long-term exposure to high LDL-C levels has an adverse effect on ASCVD [9]. The cardiovascular benefits of statins are demonstrated in a number of randomized trials, and meta-analyses of these trials established that statins are effective regardless of cardiovascular history or risk category [2,10]. Lowering LDL-C with more intensive statin regimens, and the addition of ezetimibe and PCSK9 inhibitors to standard statin therapy in cardiovascular disease has been proven to reduce the risk of ASCVD [11–13]. Therefore, each guideline sets target therapeutic values for LDL-C [14–16]. However, since LDL-C targets are not always achieved in daily practice, and there are cases where statin therapy cannot be administered due to side effects, the results of this study may be useful in real-world clinical practice.

Very low-density lipoproteins, LDL-C, and others are apo B-containing lipoproteins, and apo B lipoproteins up to a diameter of about 70 nm can pass through intact vascular endothelium, acting as atherogens [17]. Apo A1 accounts for 70 % of HDL-C and is involved in reverse cholesterol transport and anti-inflammatory properties [18]. Apo A1, apo B, and apo B/apo A1 ratio have been suggested to be more useful predictors of ischemic heart disease than HDL-C, LDL-C, and LDL-C/HDL-C ratio [19,20]. In particular, apo B/apo A1 ratio was proven to correlate with ischemic heart disease in many prospective studies [20–22]. Meanwhile, there is little information on post-PCI patients, and in this study we found an association between long-term cardiovascular events after PCI and apos.

Based on the results of the AMORIS study [20] and the INTERHEART study [21], it was proposed that an apo B/apo A1 ratio > 0.6 in women and 0.7 in men should be regarded as intermediate risk, and >0.8 in women and 0.9 in men should be regarded as high risk in the primary prevention of AMI [23]. Exercise therapy reduces apo B/apo A1 ratio by approximately 5 % in obese men [24,25], making it important in improving apos levels. Statin therapy improves apos levels, increasing apo A1 by 1–9 %, decreasing apo B by 21–44 % and apo B/apo A1 ratio by 23–46 %, with rosuvastatin being particularly useful [26–28]. Rosuvastatin with ezetimibe results in approximately 5 % decrease in apo B/apo A1 ratio compared to rosuvastatin alone [29], and the combination of atorvastatin and evolocumab reduces apo B markedly compared to atorvastatin alone [30].

In the present study, apo B and apo B/apo A1 ratio were significantly more relevant than LDL-C and LDL-C/HDL-C ratio as prognostic factors for MACE after PCI, and apo B/apo A1 ratio was also more significantly associated than LDL-C/HDL-C ratio for cardiac death and acute coronary syndrome. In a meta-analysis based on a combined primary and secondary prevention, it has been reported that apo B reduction following statin therapy is associated with a reduction in cardiovascular events independently of LDL-C lowering and that apo B reduction following non-statin therapy is also associated with a reduction in myocardial infarction [5]. In patients undergoing PCI and developing cardiovascular events, measurement of apos may trigger reevaluation of medical therapy, and intensification of medication to lower apo B may improve secondary prevention.

There are several advantages to using apos in routine practice. Although T-Cho, LDL-C, and TG are not clinically significant in the nonfasting and fasting state, T-Cho, LDL-C, and TG can change up to 8 mg/dL, 8 mg/dL, and 26 mg/dL, respectively, with dietary intake. Meanwhile, HDL-C, apo A1, and apo B do not change between nonfasting and fasting regimens [31]. In many cases, measurements are conventionally taken in fasting state owing to concern about changes in LDL-C and TG after meals. The use of apo A1 and apo B, which do not change after meals, reduces the burden on patients and medical staff. Especially in patients using diabetic

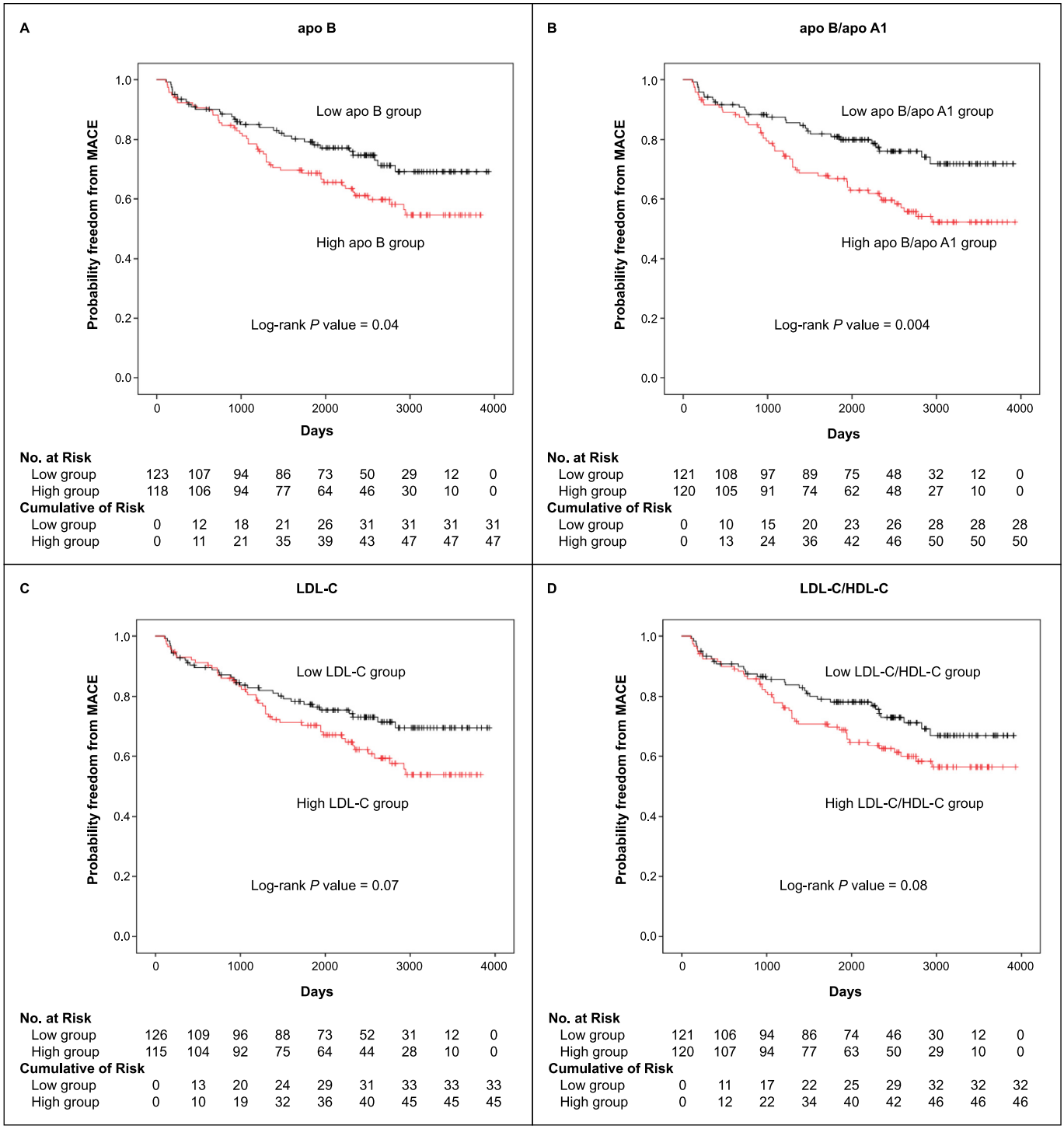

Fig. 2. The Kaplan–Meier curves divided into two groups for each blood test marker. The median case is assigned to the lower group in all groups. There are several patients with median values for apo B and LDL-C, as such, the numbers between groups differ. Apo B and apo B/apo A1 ratio groups have significant differences between the high and low groups, whereas LDL-C and LDL-C/HDL-C ratio groups lack significant differences. Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

drugs, the benefits are great for aspects such as hypoglycemia and compliance with medication.

There are several issues with apolipoproteins. Namely, there is insufficient information on the efficacy of treatment targeting apo B lowering, and even less information on apo A1 and apo B/apo A1 targeted interventions. In addition, therapeutic target values are not totally defined. Future studies are needed to resolve these issues.

5. Limitations

Firstly, this study was a single-center prospective observational study with a small sample size. Secondly, the lipid profile that could impact MACE was considered based on data obtained after medication, rather than the data at the time of the index PCI. Therefore, follow-up data were used for the analysis. In cases where MACE occurred before the

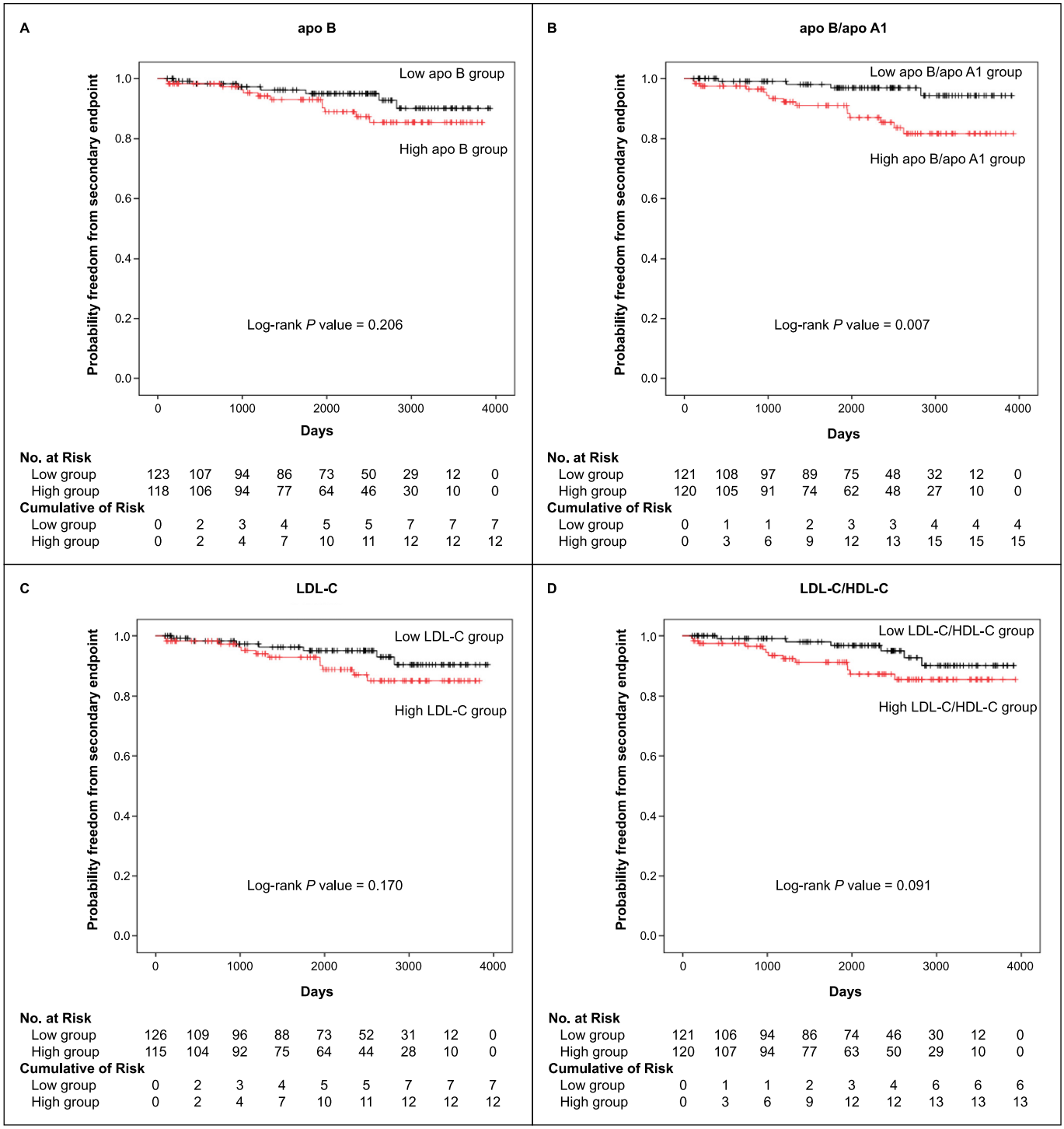

Fig. 3. The Kaplan–Meier curves with secondary endpoint. The secondary endpoint was composite of cardiac death and acute coronary syndrome. Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

follow-up CAG, we utilized the data from the time of MACE occurrence. The lipid profile undergoes temporal changes during AMI; however, the values within 24 h of onset are considered reliable as a baseline assessment [32]. Since apos are collected when follow-up CAG is performed or when MACE occurs, background data are not available for patients who have not experienced either. This may be a source of selection bias and confounding factors. Another limitation is the exclusion of stent restenosis from the events in this study, which was influenced by factors related to the procedure or the stent itself. Additionally, treatment decisions for restenosis were often made based on the physician's judgment without confirming ischemia at that time. Furthermore, it should be acknowledged that the significance of statins was not as widely recognized during the study period, leading to a low prescription rate due to requests made to primary care physicians for prescription often resulting in non-addition or

discontinuation of statin therapy because of polypharmacy. Lastly, medical therapy and indications for PCI would differ from the current situation. The results may vary when taking the maximum tolerated dose of statins.

6. Conclusions

Apo B and apo B/apo A1 ratio were found to be better prognostic predictors of long-term MACEs than LDL-C and LDL-C/HDL-C ratio in patients who have undergone PCI. The use of apos in addition to conventional lipid markers could lead to better medical therapy, resulting in prevention of recurrent ischemic heart disease.

CRediT authorship contribution statement

HK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing- Original Draft, Writing-Reviewing and Editing; KU: Conceptualization, Resource, Writing-Reviewing and Editing; AE: Formal analysis, Investigation, Visualization, Writing- Reviewing and Editing; KT: Project Administration, Resource, Supervision, Writing- Reviewing and Editing.

Data availability

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank Honyaku Center Inc. for English language editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Informed consent

Informed consent was obtained from the patient in this study.

IRB approval

Masuda Red Cross Hospital (No. 39).

References

[1] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72.
[2] Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al, Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
[3] Gotto Jr AM, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation. 2000;101:477–84.
[4] Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C, ACCESS Study Group. Atorvastatin comparative cholesterol efficacy and safety study. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. Am J Cardiol. 2001;88:265–9.
[5] Khan SU, Khan MU, Valavoor S, Khan MS, Okunrintemi V, Mamas MA, et al. Association of lowering apolipoprotein B with cardiovascular outcomes across various lipid-lowering therapies: systematic review and meta-analysis of trials. Eur J Prev Cardiol. 2020;27:1255–68.
[6] Jung HW, Hong SP, Kim KS. Comparison of apolipoprotein B/A1 ratio, TC/HDL-C, and lipoprotein (a) for predicting outcomes after PCI. PLoS One. 2021;16:e0254677.
[7] Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diab Investig. 2010;1:212–28.
[8] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227–39.
[9] Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60:2631–9.
[10] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al, Cholesterol Treatment Trialists" (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
[11] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N. Engl. J. Med. 2018;379:2097–107.
[12] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
[13] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N. Engl. J. Med. 2015;372:2387–97.
[14] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082–143.
[15] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337.
[16] Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;2019(290):140–205.
[17] Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. Curr Opin Lipidol. 2016;27:473–83.
[18] Chistiakov DA, Orekhov AN, Bobryshev YV. ApoA1 and ApoA1-specific self-antibodies in cardiovascular disease. Lab Investig. 2016;96:708–18.
[19] Sierra-Johnson J, Fisher RM, Romero-Corral A, Somers VK, Lopez-Jimenez F, Ohrvik J, et al. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. Eur Heart J. 2009;30:710–7.
[20] Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. 2001;358:2026–33.
[21] Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–52.
[22] Sniderman AD, Jungner I, Holme I, Aastveit A, Walldius G. Errors that result from using the TC/HDL C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease. J Intern Med. 2006;259:455–61.
[23] Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy–a review of the evidence. J Intern Med. 2006;259:493–519.
[24] Rosenkilde M, Rygaard L, Nordby P, Nielsen LB, Stallknecht B. Exercise and weight loss effects on cardiovascular risk factors in overweight men. J Appl Physiol. 1985;2018(125):901–8.
[25] Holme I, Høstmark AT, Anderssen SA. ApoB but not LDL-cholesterol is reduced by exercise training in overweight healthy men. Results from the 1-year randomized Oslo Diet and Exercise Study. J Intern Med. 2007;262:235–43.
[26] Blasetto JW, Stein EA, Brown WV, Chitra R, Raza A. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. Am J Cardiol. 2003.;91 (3C-10C; discussion 10C).
[27] Rader DJ, Davidson MH, Caplan RJ, Pears JS. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of rosuvastatin compared with atorvastatin, pravastatin, and simvastatin. Am. J. Cardiol. 2003;91:20C-3C; discussion 23C-4C.
[28] Takagi H, Umemoto T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A meta-analysis of randomized head-to-head trials for effects of rosuvastatin versus atorvastatin on apolipoprotein profiles. Am J Cardiol. 2014;113:292–301.
[29] Lee J, Hwang YC, Lee WJ, Won JC, Song KH, Park CY, et al. Comparison of the efficacy and safety of rosuvastatin/ezetimibe combination therapy and rosuvastatin monotherapy on lipoprotein in patients with type 2 diabetes: multicenter randomized controlled study. Diab Ther. 2020;11:859–71.

[30] Watts GF, Chan DC, Dent R, Somaratne R, Wasserman SM, Scott R, et al. Factorial effects of evolocumab and atorvastatin on lipoprotein metabolism. Circulation. 2017;135:338–51.

[31] Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al. European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) joint consensus initiative. 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.

[32] Sewdarsen M, Vythilingum S, Jialal I, Nadar R. Plasma lipids can be reliably assessed within 24 hours after acute myocardial infarction. Postgrad Med J. 1988;64:352–6.