Original article

Associations between lipid profiles and MACE in hemodialysis patients with percutaneous coronary intervention: From the FU-Registry

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ABSTRACT

Background: It is well known that percutaneous coronary intervention (PCI) in hemodialysis (HD) patients is associated with higher rates of in-stent restenosis and major adverse cardiovascular events (MACE) compared to that in non-HD patients, even if the target value in cholesterol management is achieved.
Methods: To evaluate the factors that are associated with MACE in HD patients, we selected 142 HD patients (164 lesions) without acute coronary syndrome (ACS) from 2148 patients (2568 lesions) who underwent PCI in our database of the FU-Registry [UMIN000005679, Fukuoka University Hospital EC/IRB:10-1-08(09-105)], and compared 52 patients (53 lesions) with MACE [MACE(+)] to 90 patients (111 lesions) without MACE [MACE(−)].
Results: Total cholesterol (TC: 150 ± 30 mg/dL vs 166 ± 39 mg/dL, $p < 0.05$) and high-density lipoprotein cholesterol (HDL-C: 40.1 ± 14.7 mg/dL vs 47.8 ± 13.5 mg/dL, $p < 0.01$) levels were significantly lower in the MACE(+) group at follow-up. No significant differences were observed in other parameters, including triglyceride, low-density lipoprotein cholesterol (LDL-C; LDL-C/HDL-C ratio, and % changes in HDL-C, non-HDL-C, LDL-C), and hemoglobin A1c (US National Glycohemoglobin Standardization Program) between before and after PCI. TC, LDL-C, and non-HDL-C at the time of PCI and TC, and HDL-C at the 9-month follow-up were negatively correlated with MACE, while body mass index (BMI) [odds ratio (OR): 0.81; 95% confidence interval (CI): 0.68–0.95)], prior coronary artery bypass graft (CABG) (OR: 3.89; 95%CI: 1.29–12.6), and insulin use (OR: 3.17; 95%CI: 1.23–8.55) were strongly correlated with MACE in a multivariate analysis.
Conclusion: BMI, CABG, and insulin use, but not LDL-C, are independent predictors of MACE in HD patients, suggesting that the application of lipid management for non-HD patients to HD patients at the time of PCI may not necessarily be beneficial for medium-term clinical outcomes.

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Introduction

It is well known that percutaneous coronary intervention (PCI) in hemodialysis (HD) patients is associated with higher rates of in-stent restenosis and major adverse cardiovascular events (MACE) than that in non-HD patients, even if the target value in cholesterol management is achieved [1,2]. A high level of low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease. However, in the AURORA trial [3], the LDL-C level in HD patients was not higher than that in non-HD patients, and the administration of statins in HD patients decreased LDL-C levels with no reduction in cardiovascular risk.

HD patients have characteristics that are different from those of non-HD patients. In HD patients, a decrease in lipoprotein lipase activity causes an increase in both very-low-density lipoprotein

and chylomicron remnant, and a decrease in the hepatic triacylglycerol lipase (HTGL) level leading to an increase in intermediate-density lipoprotein, resulting in a decrease in LDL-C [4]. An increase in triglyceride (TG)-rich lipoprotein contributes to the increased serum TG in HD patients [5–7]. HTGL also affects the fractional catabolic rate of apolipoprotein (apo) A–I, the major apolipoprotein of high-density lipoprotein (HDL), and an increase in the catabolic rate of apo A–I results in a low HDL-cholesterol (C) [8]. In addition, a decrease in lecithin-cholesterol acyltransferase activity also causes a decrease in HDL-C [9,10].

Therefore, based on the hypothesis that there is a large difference in the correlations between lipoprotein parameters and the incidence of MACE in chronic HD and non-HD patients who undergo PCI, we evaluated the factors that are related to MACE in HD patients who underwent PCI by comparing patients who had and did not have MACE at follow-up.

Methods

Patients

From 2148 patients (2568 lesions) who underwent PCI from January 2003 to June 2012 at Fukuoka University Hospital, Fukuoka University Chikushi Hospital, and Fukuoka White-Cross Hospital (Hakujyuji Hospital), we selected 142 HD patients who had stable angina pectoris and had undergone elective PCI (164 lesions), and divided them into a MACE(−) group (90 cases, 111 lesions) and a MACE(+) group (52 cases, 53 lesions) (Fig. 1). HD patients with acute coronary syndrome (ACS) who underwent emergent PCI were excluded. ACS included acute myocardial infarction and unstable angina. Acute myocardial infarction was diagnosed based on guidelines for the management of patients with ST-elevation myocardial infarction (JCS 2008) [11]. Myocardial infarction included both ST-elevation and non-ST-elevation types, which exhibit either distinctive ischemic electrocardiogram changes and/or elevated cardiac enzymes (creatine kinase more than twice the reference value) [11]. We performed an angiographical analysis using the database from the FU-Registry [12,13] [UMIN000005679, Fukuoka University Hospital EC/IRB:10-1-08(09-105)]. After an average of 286 days after PCI, all the patients underwent a clinical follow-up to determine the presence of MACE based on the findings at the last visit or a telephone call. Basically, all the patients who underwent PCI should have been checked by coronary angiography (CAG) after 9 months, which is the standard procedure for medical care in Japan. However, some patients did not receive CAG for various reasons and others were lost to follow-up. Therefore, we interviewed these patients over telephone. Angiographic follow-up was performed for 91.5% of all cases.

All-cause death, stent thrombus, myocardial infarction, and target lesion revascularization (TLR) were defined as MACE. TLR included ischemia-driven TLR-PCI and TLR-cardiac artery bypass graft (CABG), but did not include target lesion/vessel revascularization (TVR) or non-TVR. Further, stent thrombosis was defined to include definite, probable, and possible types according to the ARC (Academic Research Consortium) definition. If a patient had multiple lesions and had undergone PCI in each vessel with different devices at different times, the case number and event number were different, since the background would be different. However, if PCI was performed on multiple vessels at the same time, the vessel that underwent intervention first was considered to be the vessel for analysis purposes. Therefore, in such a case, the case number and event number should be the same.

Type 2 diabetes mellitus (DM) was defined as fasting glucose concentration ≥126 mg/dL, 2-h glucose ≥200 mg/dL in a 75 g oral glucose tolerance test, or non-fasting glucose ≥200 mg/dL in two separate blood tests. We also included patients who were receiving the continued oral administration of hypoglycemic agents, or who had evidently been diagnosed as having DM. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Dyslipidemia was defined as fasting levels of LDL-C ≥140 mg/dL, HDL-C <40 mg/dL, or TG ≥150 mg/dL.

PCI intravascular ultrasound

PCI was performed in patients with more than 50% significant stenosis by angiography who also showed chest symptoms or evidence of ischemia by a non-invasive test (treadmill electrocardiogram, myocardial scintigraphy). The endpoint for PCI was determined to be the absence of any dissection that might obstruct blood flow to achieve thrombolysis in myocardial infarction (TIMI) III flow with 10% or less angiographic stenosis, which was determined based on daily clinical practice. Intravascular ultrasound (IVUS) was used in 40% of the cases, since we used IVUS for stent inflation and to assay the minimum lumen area, but data were available in only 659 of 2568 lesions (25.7%). Since the results of pre-procedural IVUS included many cases in which IVUS could not be passed through lesions, these cases were not included in the present analysis and only the results of post-procedural IVUS were used.

Medication (antiplatelets)

With regard to the use of antiplatelets, the administration of aspirin (100 mg) and 200 mg of ticlopidine or 75 mg of clopidogrel was started in all cases at least 48 h before stent insertion. In principle, antiplatelets other than aspirin were administered continuously for at least 2 weeks in patients with a bare metal stent and all antiplatelets were administered for at least nine months after PCI in patients with an indwelling drug-eluting stent (DES).

Quantitative coronary angiography

Quantitative coronary angiography (QCA) was performed in 1,775 of 2,568 lesions (69.1%). QCA data were not available for all of the lesions because (1) follow-up CAG was not performed both in our hospital and two other collaborating hospitals, or (2) lesions for QCA analyses were randomly selected during the period when we started to establish a QCA analysis system (between 2003 and 2005). Quantitative and qualitative analyses were performed using CMS-GFT (MEDES, Amsterdam, The Netherlands) at Fukuoka University, which was the core laboratory for the study, as described previously [13–17]. An analysis was performed for angiograms obtained at pre-procedural and post-procedural

Outline of the study

2,148 cases (2,568 lesions)

Non-hemodialysis patients and those with ACS were excluded.

142 cases (164 lesions)

MACE(-) group
90 cases (111 lesions)

MACE(+) group
52 cases (53 lesions)

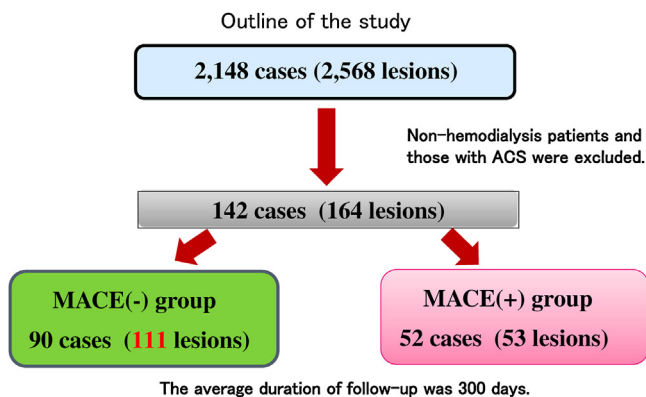The average duration of follow-up was 300 days.

Fig. 1. Outline of the study (the FU-Registry). ACS, acute coronary syndrome; MACE, major adverse cardiovascular events.

follow-up. All measurements were performed based on angiography after the intracoronary injection of nitroglycerin. Segments were defined as the in-stent region, the proximal edge of the stent, and a region 5.0 mm from the distal edge, respectively. A late loss was defined as the difference in the minimum lesion diameter between the post-procedural angiogram and the follow-up angiogram. In addition, restenosis was defined as a stenosis rate of 50% or higher, as described previously [13].

Statistical data analysis

We collected the data in a Filemaker Pro database and then exported into an Excel spreadsheet for analysis. Statistical data analysis was performed using SAS software (Version 9.1 SAS Institute, Cary, NC, USA) at Fukuoka University. The chi-square test was used to compare categorical variables between groups. The Wilcoxon rank-sum test and Student *t*-test were used to compare continuous variables between groups, which were expressed as the mean ± SD. Correlations between variables were examined by the Spearman correlation. The associations between the predictor variables at the time of PCI with MACE were examined by a simple logistic regression analysis. The independence of the associations among the predictor variables at the time of PCI that were associated with MACE was examined by a multiple logistic regression analysis, and variables included in the model were selected using the Score selection method [18]. The multicollinearity of explanatory variables was diagnosed using a regression analysis [19]. A value of $p < 0.05$ was considered to reflect statistical significance.

Results

With regard to the patient background, the MACE(+) group showed significantly lower percentages of ultrasound cardiography-LVEF (53.0% vs 58.6%, $p = 0.02$) and lower levels of TC (158 ± 34 mg/dL vs 173 ± 44 mg/dL, $p = 0.03$), LDL-C (90 ± 25 mg/dL vs 104 ± 36 mg/dL, $p = 0.01$), and uric acid (5.3 ± 1.8 mg/dL vs 6.1 ± 1.7 mg/dL, $p = 0.07$) at the PCI procedure, compared to the MACE(−) group (Table 1). Although no difference in albumin was observed between the groups, BMI was significantly lower (20.3 ± 2.3 kg/m² vs 21.5 ± 3.8 kg/m², $p = 0.02$) in the MACE(+) group. With regard to prior/complicating disease, the MACE(+) group had significantly ($p < 0.01$) higher percentages of prior MI and prior CABG.

While BMI at the time of PCI follow-up (after an average of 286 days) was also significantly lower (20.0 ± 1.8 kg/m² vs 21.1 ± 3.2 kg/m², $p = 0.01$) in the MACE(+) group, there were no significant differences in the percent reduction in BMI. At the follow-up, TC (150 ± 30 mg/dL vs 166 ± 39 mg/dL, $p = 0.02$) and HDL-C (40.1 ± 14.7 mg/dL vs 47.8 ± 13.5 mg/dL, $p = 0.01$) in the MACE(+) group were significantly lower than those in the MACE(−) group. No significant differences were observed in other parameters, including TG, LDL-C, L/H ratio, or % changes in HDL-C, non-HDL-C, LDL-C, or HbA1c (Table 1).

At the time of PCI, there was no difference in the % use of antihypertensive drugs or statin drugs, or in the percentage of patients with DM between the groups, while the MACE(+) group showed a significantly higher percentage of insulin use (44.2% vs 24.4%, $p = 0.02$). The MACE(+) group also showed significantly higher use rates for nitrates and insulin at the time of follow-up (Table 2).

As shown in Table 3, among the lesion characteristics, while there was no significant difference in the percentage of extensive calcification, the MACE(+) group showed significantly higher percentages of pre-in-stent restenosis (49.1% vs 31.5%, $p < 0.05$) and left main trunk lesions (26.4% vs 4.5%, $p < 0.001$), and a tendency for a lower rate of use of DES (47.2% vs 64.9%, $p = 0.10$). The results of pre- and post-procedural QCA and IVUS were similar in the two groups (Table 3). With regard to the clinical outcome,

Table 1
Patient characteristics and results of blood tests at PCI procedure and follow-up.

	MACE(−) ($n = 90$)	MACE(+) ($n = 52$)
Clinical characteristics at PCI procedure		
Mean age (years)	69.5 ± 8.7	68.5 ± 7.4
BMI (kg/m²)	21.5 ± 3.8	20.3 ± 2.3 *
Male (%)	70.0	75.0
SBP (mmHg)	137.6 ± 23.8	138.5 ± 26.4
DBP (mmHg)	70.4 ± 13.9	68.7 ± 13.0
Pulse rate (/min)	75.9 ± 11.6	78.4 ± 11.4
UCG-LVEF (%)	58.6	53.0 *
Clinical characteristics at follow-up		
BMI (kg/m²)	21.1 ± 3.2	20.0 ± 1.8 *
BMI percent change (%)	0.97	0.67
LVEF-UCG (%)	56.8	52.6
Blood tests at PCI procedure		
ALB (mg/dL)	3.9 ± 0.5	3.8 ± 1.0
UA (mg/dL)	6.1 ± 1.7	5.3 ± 1.8 †
TC (mg/dL)	173 ± 44	158 ± 34 *
TG (mg/dL)	121 ± 66	122 ± 82
HDL-C (mg/dL)	45.4 ± 13.3	43.1 ± 12.3
Non-HDL-C (mg/dL)	128 ± 41	116 ± 33
LDL-C (mg/dL)	104 ± 36	90 ± 25 *
LDL-C/HDL-C	2.5 ± 1.0	2.3 ± 0.8
HbA1c (%)	6.0	5.9
Blood tests at follow-up		
ALB (mg/dL)	3.5 ± 0.2	3.1 ± 0.3
TC (mg/dL)	166 ± 39	150 ± 30 *
TG (mg/dL)	117 ± 60	127 ± 70
HDL-C (mg/dL)	47.8 ± 13.5	40.1 ± 14.7 †
LDL-C (mg/dL)	94 ± 33	84 ± 26
LDL-C/HDL-C	2.14	2.43
Non-HDL-C (mg/dL)	117 ± 37	110 ± 27
LDL-C percent change (%)	−4.9	−6.9
HDL-C percent change (%)	9.4	−1.5
Non-HDL-C percent change (%)	−1.3	−2.9
HbA1c (%)	6.0 ± 1.2	6.2 ± 1.1
Prior complicating diseases		
Prior PCI (%)	54.4	71.2
Prior CABG (%)	8.9	28.8 †
Prior MI (%)	23.3	46.2 †
ASO (%)	24.4	25.0
Hypertension (%)	82.2	80.8
Hyperlipidemia (%)	44.4	40.4
Type 2 diabetes (%)	62.2	75.0

NSGP value was presented for HbA1c.
MACE: major adverse cardiovascular events; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; UCG LVEF: ultrasound cardiography left ventricle ejection fraction; ALB: albumin; UA: uric acid; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; non-HDL-C: non-high density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; L/H ratio: LDL-C/HDL-C; HbA1c: hemoglobin A1c; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; MI: myocardial infarction; ASO: arteriosclerosis obliterans; TC percent change = {TC (follow-up) − TC (pre)}/TC (pre) × 100; LDL-C percent decrease = {LDL-C (follow-up) − LDL-C (pre)}/LDL-C (pre) × 100; HDL-C percent increase = {HDL-C (follow-up) − HDL-C (pre)}/HDL-C (pre) × 100; non-HDL-C percent decrease = {non-HDL-C (pre) − non-HDL-C (follow-up)/non-HDL-C (pre) × 100.
* $p < 0.05$.
† $p < 0.01$.

the frequencies of MACE, i.e. TLR-PCI, death, stent thrombus, MI, and TLR-CABG, were 80.8%, 15.4%, 13.5%, 9.6%, and 3.9%, respectively (Table 4).

In a univariate analysis of the relations between lipoprotein parameters and MACE, negative relations were seen among MACE and TC, LDL-C, and non-HDL-C at the time of PCI, as well as TC and HDL-C at the time of follow-up. The independence of the association among the predictor variables at the time of PCI that were associated with MACE was examined by a multiple logistic regression analysis with the following models – Model 1: single LDL-C; Model 2: single LDL-C + BMI; Model 3: single LDL-C + prior CABG; Model 4: single LDL-C + insulin use; Model 5: single LDL-C + BMI + prior CABG

Table 2
Medications at PCI procedure and follow-up.

	MACE(−) (n = 90)	MACE(+) (n = 52)
Medications at PCI procedure		
Ca blocker (%)	51.1	50.0
ACEI (%)	11.2	7.7
B-blocker (%)	13.3	17.3
Statin (%)	26.7	36.5
Nitrate (%)	40.0	36.5
ARB (%)	41.1	50.0
Nicorandil (%)	40.0	36.5
Insulin (%)	24.4	44.2*
DPP-4 inhibitor (%)	2.2	0
Medications at follow-up		
Ca blocker (%)	44.4	55.8
ACEI (%)	6.7	11.6
B-blocker (%)	14.4	19.2
Statin (%)	38.9	38.5
Nitrate (%)	33.3	57.7†
ARB (%)	43.3	48.1
Nicorandil (%)	27.8	42.3
Insulin (%)	24.4	46.2*
DPP-4 inhibitor (%)	1.1	0

MACE: major adverse cardiovascular events; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DPP-4 inhibitor: dipeptidyl peptidase-4 inhibitor.
* $p < 0.05$.
† $p < 0.01$.

+ insulin use. As a result, BMI [odds ratio (OR): 0.81 (95%CI: 0.68–0.95)], prior CABG [OR: 3.89 (95%CI: 1.29–12.6)] and insulin [OR: 3.17 (95%CI: 1.23–8.55)] were independently associated with MACE (Table 5). LDL-C was not significantly associated with MACE after adjusting for BMI, prior CABG, and insulin in HD patients.

Table 3
Lesion characteristics and pre- and post-procedural QCA results.

	MACE(−) n = 111	MACE(+) n = 53
Lesion characteristics		
3-vessel disease (%)	50.4	58.5
RCA/LAD/Cx (%)	35.1/42.3/22.6	35.7/45.2/19.1
Pre-in-stent restenosis (%)	31.5	49.1*
AHA/ACC type B2+C (%)	72.9	77.4
Severe calcification (%)	36.0	47.2
DES (%)	64.9	47.2
LMT (%)	4.5	26.4†
	n = 56	n = 30
Pre-procedural QCA results		
Lesion length (mm)	17.4 ± 9.7	19.3 ± 15.9
Angulation (%)	28.8	31.7
Reference (mm)	2.7 ± 0.8	2.5 ± 0.6
MLD (mm)	0.7 ± 0.5	0.7 ± 0.3
%DS (%)	70.4	71.6
	n = 56	n = 30
Post-procedural QCA results		
Reference (mm)	2.6 ± 0.6	2.6 ± 0.6
MLD (mm)	2.0 ± 0.6	2.0 ± 0.6
%DS (%)	28.1	24.8
Stent length (mm)	24.3 ± 13.1	21.5 ± 13.7
Stent reference (mm)	2.9 ± 0.5	2.8 ± 0.5
Stent MLD (mm)	2.5 ± 0.5	2.4 ± 0.5
Stent %DS (%)	14.9	12.1

MACE: major adverse cardiovascular events; RCA: right coronary artery; LAD: left anterior descending; Cx: left circumflex branch; MLD: minimum lumen diameter; %DS: percent diameter stenosis; IVUS: intravascular ultrasound; CSA: cross-sectional area; EEM: external elastic membrane.
* $p < 0.05$.
† $p < 0.01$.

Table 4
Lesion characteristics, follow-up QCA results, and clinical outcomes.

	MACE(−) n = 97	MACE(+) n = 53
Angiographic follow-up results		
In-stent restenosis (%)	9.3	90.6‡
	N = 40	N = 21
Follow-up QCA		
Lesion late loss (mm)	0.20 ± 0.61	0.95 ± 0.87
Lesion %DS (%)	28.5	71.0
	n = 90	n = 52
Clinical outcomes (MACE)		
Stent thrombus (%)	0	13.5
Death (%)	0	15.4
MI (%)	0	9.6
TLR-PCI (%)	0	80.8
TLR-CABG (%)	0	3.9

MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR-PCI: target lesion restenosis-percutaneous coronary intervention; TLR-CABG: target lesion restenosis-cardiac artery bypass graft.
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

Discussion

It is well known that medium- and long-term clinical outcomes can be affected by an abnormal lipid metabolism in the primary and secondary prevention of coronary artery disease. However, in the AURORA trial [3], in which 2776 HD patients were divided into a placebo group and a treatment group that received rosuvastatin at 10 mg/day, the combined endpoint of events such as cardiovascular death, non-fatal MI, and non-fatal cerebral vascular disorder was not significantly reduced in the treatment group, with a decrease of only 4%. In addition, in 2005, the 4D study, in which 1255 HD patients with DM were randomly assigned to receive either 20 mg of atorvastatin per day or matching placebo, did not show a significant reduction in the primary endpoint [20]. The SHARP trial was conducted in 9720 patients with chronic kidney disease (CKD) with no known history of cardiovascular disease, and 33% of the patients were on HD [21]. Patients were assigned to receive either simvastatin 20 mg plus ezetimibe 10 mg daily or placebo with a median follow-up of 4.9 years. This combination therapy reduced the incidence of major atherosclerotic events in a wide range of patients with CKD. After the researchers adjusted for the reduction in LDL-C, the proportional reductions in major atherosclerotic events per 1 mmol/L reduction in LDL-C were similar for stage 4 and 5 CKD patients; however, the subgroup of patients with dialysis showed no significant benefit with treatment [21]. These findings suggest that we should not expect to see an overall decrease in the risk of cardiovascular disease for patients who are receiving HD therapy under lipid-lowering therapy based on statins.

Very few registry studies or non-statin trials have investigated the factors that are related to MACE in HD patients who underwent PCI. In the present study, we divided stable angina patients who were receiving maintenance HD into two groups according to the presence or absence of MACE, and examined the relation between the LDL-C level and MACE. Although the MACE(+) group showed a significantly lower LDL-C level at PCI (Table 1), the LDL-C level was not independently associated with MACE in a multivariate analysis. Further, an examination of the correlation between statin use and MACE showed an OR of 1.27 (95%CI: 0.54–2.9) (data not shown), and thus we could not confirm the effectiveness of

Table 5
Multivariate logistic regression analysis of the independent predicting factor for MACE in HD patients.

	Odds ratio (95% confidence Intervals)				
	Model 1	Model 2	Model 3	Model 4	Model 5
LDL-C	0.99 (0.97–1.00)*	0.99 (0.97–1.00)	0.99 (0.98–1.00)	0.99 (0.97–1.00)	0.99 (0.98–1.01)
BMI		0.88 (0.76–1.01)			0.81 (0.68–0.95)*
Prior CABG			3.13 (1.15–8.96)*		3.89 (1.29–12.6)*
Insulin				2.40 (1.03–5.59)*	3.17 (1.23–8.55)*

Model 1: single LDL-C (at the time of PCI).
Model 2: LDL-C (at the time of PCI) + BMI (at the time of PCI).
Model 3: LDL-C (at the time of PCI) + Prior CABG (at the time of PCI).
Model 4: LDL-C (at the time of PCI) + Insulin (at the time of PCI).
Model 5: LDL-C (at the time of PCI) + BMI (at the time of PCI) + Prior CABG (at the time of PCI) + Insulin use (at the time of PCI).
MACE: major adverse cardiovascular events, CABG: coronary artery bypass graft, BMI: body mass index, LDL-C: Low density lipoprotein-cholesterol.
* $p < 0.05$.

statins that is consistent with the results of the AURORA and 4D trials.

Since LDL-C is generally an important risk factor for MACE, as shown in the MEGA [22], MEGA-CKD [23], and other studies [24], we compared the associations between lipoprotein parameters and the incidence of MACE in 1578 non-HD patients with stable angina (number of lesions: 1,909, pre-LDL-C: 106 ± 48 mg/dL, post-LDL-C: 93 ± 29 mg/dL) to the results in 142 HD patients in our FU-Registry analysis (Fig. 2A). The results showed that the LDL-C level, TC, and non-HDL-C were significantly associated with MACE (Fig. 2A), but
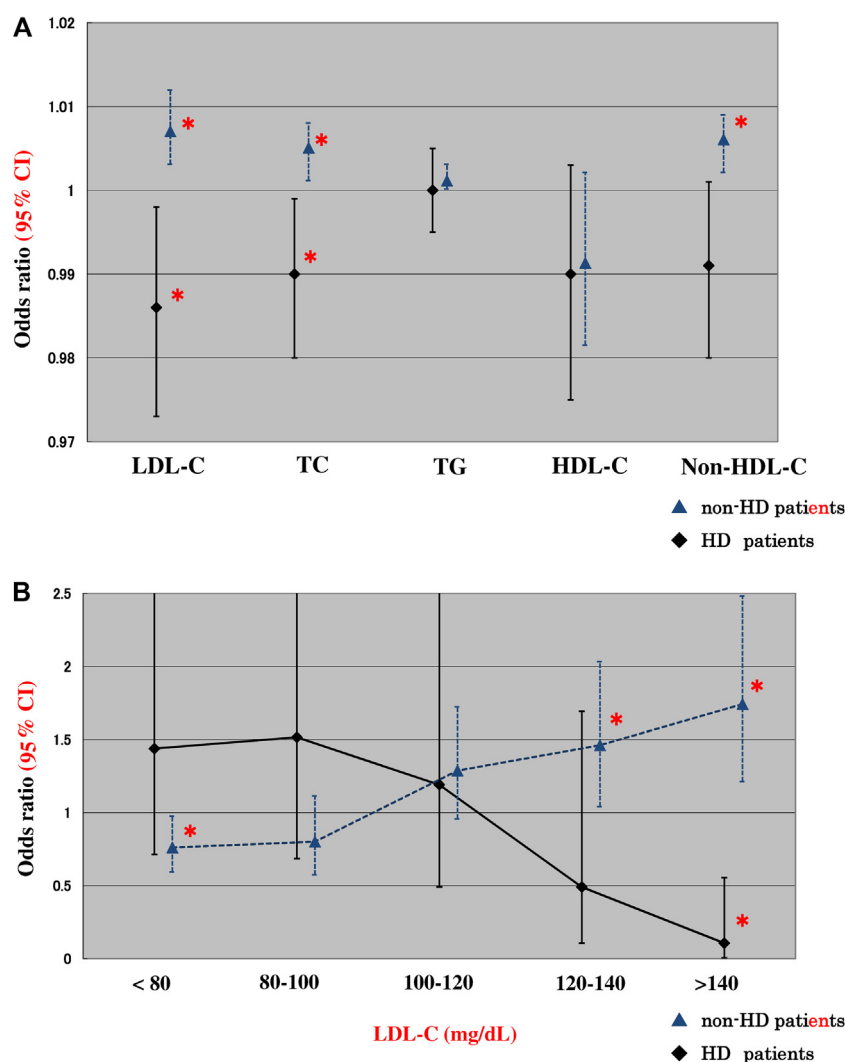
Fig. 2. (A) The associations between lipid and lipoprotein parameters and the incidence of MACE in 1578 non-HD patients and 142 HD patients with stable angina. Data are presented as odds ratio (95% confidence interval). *$p < 0.05$, assessed by logistic regression analysis. (B) The association between LDL-C and the incidence of MACE. LDL-C was stratified into five groups (LDL-C < 80 mg/dL, 80–100 mg/dL, 100–120 mg/dL, 120–140 mg/dL, and 140 mg/dL < LDL-C) in 1578 non-HD patients and 142 HD patients with stable angina. Data are presented as odds ratio (95% confidence interval). *$p < 0.05$, assessed by logistic regression analysis. LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HD, hemodialysis.

the relation observed in non-HD patients was opposite to that seen in HD patients. We stratified the patients into five groups according to the LDL-C level (LDL-C < 80 mg/dL, 80–100 mg/dL, 100–120 mg/dL, 120–140 mg/dL, and >140 mg/dL), and the relation between LDL-C and the incidence of MACE was investigated in each group (Fig. 2B). The results showed that the LDL-C-associated risk of MACE increased as the LDL-C level increased in the non-HD group, and was negative in patients with LDL-C < 80 mg/dL and positive in patients with LDL-C 120–140 mg/dL and 140 mg/dL. In contrast to non-HD patients, we found that the risk of MACE tended to decrease with an increase in the LDL-C value in HD patients, and was negative in patients with LDL-C > 140 mg/dL. Even though our study focused on the outcome of PCI with/without HD, and our registry is not a cholesterol-lowering intervention, we can at least conclude that lipid management in HD patients with PCI should be different from that in non-HD patients if we also consider the data from previous studies.

Ikewaki et al. [25] reported that LDL and LDL-apoB remain in the blood almost twice as long in HD patients as in normal subjects due to a reduced catabolic rate of apo B, such as that associated with a reduction in LDL being taken up into the liver. Therefore, LDL in HD patients is prone to be modified by oxidation or denaturation in blood vessels, which suggests that large amounts of such modified LDL circulate in the blood of HD patients. While we previously reported that fast-migrating (modified or electronegative) LDL [26–28] was increased in HD patients, plasma TC and slow-migrating (not modified or electropositive) LDL fractions were within the normal range in such patients. In addition, it has also been reported that the amount of time that LDL remains in the blood is extended in CKD as the disease progresses [29]. An in vitro experiment suggested that regulation of the pro-apoptotic protein BAD by uremic toxins may increase cardiovascular toxicity [30]. Thus, such patients under maintenance HD are in a uremic state and the duration of exposure to uremia is directly related to the duration of HD. Lowering of the serum LDL-C level may not adequately reduce the risk, and current target values in lipid management may not be useful for preventing MACE in HD. More comprehensive management schemes that do not involve statin/lipid control but rather seek to lower BMI or insulin use, or prior PCI, based on our findings in a multivariate analysis, should be the focus for HD patients with PCI [31].

It has also been reported that, in systemic erythematosus, chronic inflammation (high C-reactive proteinemia) is associated with the development of new cardiovascular disease [32], and C-reactive protein levels predict restenosis and MACE after PCI in both non-dialysis patients [33,34] and HD patients [35]. Therefore, increased inflammatory cytokine levels caused by maintenance HD may induce neointimal proliferation at sites where PCI was performed, which could promote MACE. The changes in lipoprotein parameters including LDL-C, HDL-C, non-HDL-C, etc., might just be secondary factors caused by the chronic inflammation.

Our study has some limitations. Since the present study is a retrospective analysis of patients who underwent PCI from January 2003 to June 2012, the results may need to be further supported by prospective analyses. Since the total number of HD patients was 142, changes in long-term clinical outcomes may also need to be confirmed by increasing both the total number of patients and the duration of follow-up. Factors such as HD duration, hemoglobin levels, Ca, P and so on greatly affect adverse events in the dialysis population. In our FU-Registry, while we did not include such parameters, we did consider albumin, and no difference in albumin levels was observed between the MACE(+) and MACE(−) groups (Table 1). We did not examine the effects of different types of DES, which were used in our registry during 2003–2012, on MACE in HD patients. Even if a DES including sirolimus- or paclitaxel-eluting stents or recent second-generation stents is used, definite evidence

that DES reduce MACE in HD patients may not be anticipated, as reported [36–38].

In conclusion, BMI, prior CABG, and insulin use, but not LDL-C, are independent predictors of MACE in HD patients, suggesting that the application of lipid management for non-HD patients to HD patients at the time of PCI may not necessarily be beneficial for medium-term clinical outcomes.

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