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Prolonged dual antiplatelet therapy in invasively treated acute coronary syndrome patients with different lipoprotein(a) concentrations

Kongyong Cui[1, 2, 3]*, Shaoyu Wu[1, 2, 3]*, Dong Yin[1, 2, 3], Weihua Song[1, 2, 3], Hongjian Wang[1, 2, 3], Chenggang Zhu[1, 2, 3], Lei Feng[1, 2, 3], Yuejin Yang[1, 2, 3], Rui Fu[1, 2, 3#], Kefei Dou[1, 2, 3#]

[1]Department of Cardiology, Cardiometabolic Medicine Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[2]State Key Laboratory of Cardiovascular Disease, Beijing, China
[3]National Clinical Research Center for Cardiovascular Diseases, Beijing, China

Abstract

Background: *Lipoprotein(a) [Lp(a)] was positively associated with recurrent ischemic events in patients with acute coronary syndrome (ACS). This study was performed to investigate the effect of Lp(a) levels on outcomes of dual antiplatelet therapy (DAPT) > 1 year versus DAPT ≤ 1 year after percutaneous coronary intervention (PCI) in this population.*

Methods: *A total of 4,357 ACS patients who were event-free at 1 year after PCI were selected from the Fuwai PCI Registry, and patients were stratified into four groups according to DAPT duration (≤ 1 year vs. > 1 year) and Lp(a) levels (≤ 30 mg/dL vs. > 30 mg/dL). The primary endpoint was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of cardiac death, myocardial infarction or stroke.*

Results: *After 2.4-year follow-up, the incidence of MACCE (hazard ratio [HR]$_{adjusted}$ 0.284, 95% confidence interval [CI] 0.115–0.700; HR$_{IPTW}$ 0.351, 95% CI 0.164–0.751) were significantly reduced in DAPT > 1 year group than that in DAPT ≤ 1 year group in individuals with elevated Lp(a) levels. However, in individuals with normal Lp(a) levels, no statistically difference was found between these two groups in terms of MACCE, although the risks of all-cause death and definite/probable stent thrombosis were lower in DAPT > 1 year group. Notably, the risk of clinically relevant bleeding did not statistically differ between these two groups in individuals with different Lp(a) levels.*

Conclusions: *This study firstly demonstrated that extended DAPT (> 1 year) was statistically associated with lower risk of ischemic events in ACS patients with elevated Lp(a) levels after PCI, whereas this association was not found in individuals with normal Lp(a) levels.* (Cardiol J 2024; 31, 1: 32–44)

Keywords: lipoprotein(a), acute coronary syndrome, percutaneous coronary intervention, drug-eluting stent, dual antiplatelet therapy, prognosis

Address for correspondence: Rui Fu, MD and Kefei Dou, MD, Department of Cardiology, Cardiometabolic Medicine Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167, Beilishi Road, Xicheng District, Beijing 100037, China, fax: +86-10-6831-3012, tel: +86-10-8832-2562 and +86-10-8839-6590, e-mail: fwfurui@163.com and drdoukefei@126.com

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**Drs. Kongyong Cui and Shaoyu Wu contributed equally to this article and shared the first author.*
#Drs. Rui Fu and Kefei Dou contributed equally to this article.

Introduction

Lipoprotein(a) [Lp(a)] is an atherogenic low-density lipoprotein (LDL) subspecies, consisting of an LDL-like particle which apolipoprotein B100 is covalently linked to apolipoprotein(a) [apo(a)] [1, 2]. Over the last 10 years, genetic and epidemiologic evidence supported that high Lp(a) level was a risk factor for cardiovascular disease [3–6]. Moreover, previous studies, including the present authors, revealed that Lp(a) was positively associated with recurrent cardiovascular events in patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI) [7–10]. However, there are no approved pharmacologic therapies that are specifically aimed at lowering Lp(a) levels. Actually, Lp(a) may result in a prothrombotic state due to the high degree of homology between apo(a) and plasminogen [2]. The ASPREE trial including 12,815 individuals showed that acetylsalicylic acid (ASA) may benefit older individuals with elevated Lp(a) genotypes in primary prevention [11]. In addition, similar results were obtained in the Women's Health Study [12]. Dual antiplatelet therapy (DAPT) with ASA plus a $P2Y_{12}$ inhibitor is prescribed for the prevention of thrombotic complications for patients with ACS after PCI. Current guidelines on DAPT from the United States and Europe recommend DAPT for ≥ 12 months after PCI in ACS patients who have tolerated DAPT without a bleeding complication and who are not at high-risk of bleeding [13]. Given the pathophysiological effect of apo(a), was speculated herein, that the extended duration of DAPT after PCI may reduce the risk of ischemic events for ACS patients who had elevated Lp(a) levels. Therefore, this study was performed to evaluate the impact of Lp(a) levels on clinical outcomes of extended DAPT (> 1 year) versus shortened DAPT (≤ 1 year) in ACS patients who underwent PCI with drug-eluting stent (DES).

Methods

Study design and population

This was a secondary analysis of a single-center, prospective registry and details on the study design have been published elsewhere [7, 14–16]. Briefly, 10,724 patients with coronary artery disease (CAD) who underwent PCI were consecutively enrolled between January 2013 and December 2013 from FuWai Hospital, National Center for Cardiovascular Diseases. The study was performed according to the principles of the Declaration of Helsinki and the study protocol had been approved by the ethical committee of Fuwai Hospital, National Center for Cardiovascular Diseases. All the participants provided written informed consent before enrollment. In addition, patient records were anonymized and de-identified before database merging and analysis.

In this paper, 3,607 patients with stable CAD, 28 patients who did not receive DAPT, 369 patients who did not use DES, and 848 patients who experienced major adverse events (death, myocardial infarction [MI], stent thrombosis [ST], stroke, repeat revascularization, or Bleeding Academic Research Consortium [BARC] type 2, 3 or 5 bleeding) within 1 year follow-up were excluded. In addition, 1,515 patients were excluded due to the reasons listed in Figure 1. For the final analysis, 4,357 ACS patients who were event-free at 1 year after PCI were evaluated.

Study procedures and biochemical analysis

After an overnight fasting before PCI, laboratory samples were obtained from each participant and all tests were performed through clinical chemistry department of the present center. Concentrations of Lp(a), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol were analyzed with the automated biochemical analyzer (Hitachi 7150, Tokyo, Japan), while hemoglobin A1c was measured with the Tosoh Automated Glycohemoglobin Analyser (HLC-723G8; Tosoh Corporation, Tokyo, Japan). Measurements were Lp(a) by the immunoturbidimetry method [LASAY Lp(a) auto; SHIMA Laboratories Co., Ltd, Tokyo, Japan] with a normal cutoff value of < 30 mg/dL. An Lp(a) protein validated standard was used to calibrate the examination, and the coefficient of variation for repetitive measurements was < 10% [17].

During hospitalization, all procedures and medical therapies were performed in compliance with contemporary guideline recommendations and the cardiologist's discretion. Demographics, cardiovascular risk factors, clinical parameters, laboratory results, angiographic and procedural details, and medications were prospectively recorded in our dedicated PCI registry by independent research personnel. Definitions of diabetes, hypertension, dyslipidemia and other variables were in compliance with previous studies [7, 15, 16].

Based on DAPT duration, patients were divided into DAPT > 1 year group and DAPT ≤ 1 year group. Notably, previous meta-analyses and current Chinese guidelines for the management

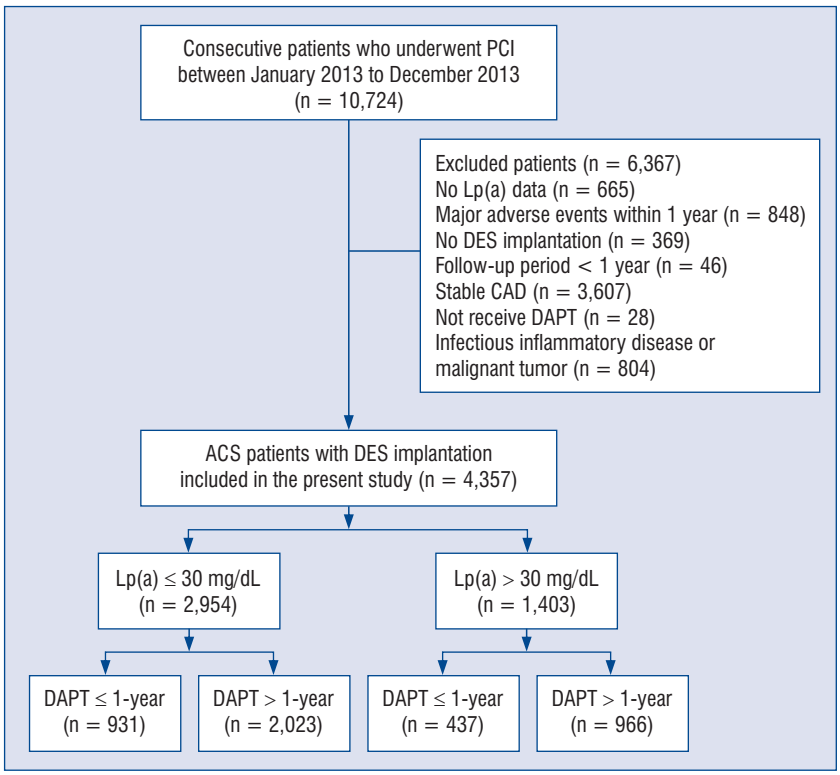

Figure 1. Flow chart of the study; ACS — acute coronary syndrome; CAD — coronary artery disease; DAPT — dual antiplatelet therapy; DES — drug-eluting stent; PCI — percutaneous coronary intervention.

of dyslipidemia in adults suggested that Lp(a) concentrations > 30 mg/dL were associated with a progressive increase in the incidence of cardiovascular events [1, 4, 18, 19]. In this paper, a threshold value of 30 mg/dL was used to assign abnormal Lp(a) levels. Then, patients were stratified into four groups according to the DAPT duration (≤ 1 year vs. > 1 year) and Lp(a) levels (≤ 30 mg/dL vs. > 30 mg/dL).

Follow-up and endpoints

After PCI, patients were followed up at 6-month intervals until January, 2016. Data for endpoints were collected from medical records, clinical visits, and/or telephone interviews by trained investigators who were blind to the clinical data. Of note, adherence to antiplatelet medication was routinely assessed at each time of follow-up, and the status of antiplatelet therapy was collected by dedicated questionnaires and the electronic prescribing system at the present center. The primary endpoint was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of cardiac death, nonfatal MI or stroke. The individual components of the primary endpoint, all-cause death, definite or probable ST, and BARC type 2, 3 or 5 bleeding were secondary endpoints. All deaths were considered to be cardiac-related unless a non-cardiac origin was documented. MI was defined based on the Third Universal Definition of MI [20]. Stroke was defined as new focal neurological deficit lasting > 24 hours and confirmed by imaging evidence. Definite or probable ST was adjudicated based on the Academic Research Consortium criteria [21]. In addition, bleeding events were categorized based on the BARC classifications [22]. All events must be validated by source documents.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and differences in various characteristics were compared using the Student's t-test or Wilcoxon's rank sum test, when appropriate. Categorical variables were expressed as frequencies (percentages) and compared using Pearson's chi-square test or the Fisher exact test, when appropriate. Cumulative incidence of clinical outcomes was estimated using Kaplan-Meier curves, and differences were evaluated with the log-rank test. Univariable and multivariable Cox regression analyses were performed to calculate

hazard ratios (HRs) and 95% confidence intervals (CIs). In addition, an inverse probability of treatment weighting (IPTW) analysis was also conducted to adjust for differences in baseline characteristics between DAPT ≤ 1 year and DAPT > 1 year groups in overall population, individuals with normal Lp(a) levels, and individuals with elevated Lp(a) levels, respectively. A propensity score was developed using a non-parsimonious multivariable logistic regression model and considering DAPT time (DAPT > 1 year vs. DAPT ≤ 1 year) as the dependent variable. Covariates used for the propensity score model and multivariable Cox regression model were age, gender, body mass index, current smoking, diabetes, hypertension, dyslipidemia, previous MI, previous stroke, peripheral vascular disease, left ventricular ejection fraction < 50%, LDL-C, HDL-C, radial artery access, multivessel disease, severe calcification, total lesion length, minimum stent diameter, total stent length, and use of statin at discharge. All statistical analyses were conducted using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value of < 0.05 was considered to indicate statistical significance.

Results

Of the eligible participants, 1,368 received DAPT ≤ 1 year and 2,989 received DAPT > 1 year, while 2,954 had normal Lp(a) levels and 1,403 had elevated Lp(a) levels (Fig. 1). Overall, patients who received DAPT > 1 year were more likely to have a history of dyslipidemia, multivessel disease, severe calcification, and smaller minimum stent diameter during PCI than those who received DAPT ≤ 1 year. Furthermore, at any time-point of follow-up, the use of ASA and $P2Y_{12}$ receptor inhibitor was significantly more frequent in DAPT > 1 year group than that in DAPT ≤ 1 year group (**Suppl. Table S1**). As shown in Table 1, baseline patient, angiographic and procedural characteristics were mostly similar between DAPT ≤ 1 year and DAPT > 1 year groups in both patients with normal Lp(a) levels and elevated Lp(a) levels. Similar to the overall ACS population, patients in DAPT > 1 year group were more likely to receive ASA and $P2Y_{12}$ receptor inhibitor than those in DAPT ≤ 1 year group in both patients with normal Lp(a) levels and elevated Lp(a) levels at any time-point of follow-up. The median follow-up period was 877 (807–942) days.

DAPT duration and clinical outcomes

Compared with patients who received DAPT ≤ 1 year, those who received DAPT > 1 year presented lower risks of MACCE, all-cause death, cardiac death, and definite/probable ST (Fig. 2; **Suppl. Table S2**). In Figure 3, all the candidate variables were well balanced between the DAPT ≤ 1 year group and DAPT > 1 year group after IPTW analysis. The risks of MACCE, all-cause death, cardiac death, and definite/probable ST were also significantly lower in extended DAPT group than that in shortened DAPT group. Notably, no significant difference was found between the two groups in terms of clinically relevant bleeding (**Suppl. Table S2**).

Extended DAPT vs. shortened DAPT in patients with different Lp(a) levels

In individuals with elevated Lp(a) levels, the incidence of 2.4-year MACCE was significantly lower in DAPT > 1 year group than that in DAPT ≤ 1 year group (1.2% vs. 2.7%; adjusted HR 0.284, 95% CI 0.115–0.700). In addition, patients in DAPT > 1 year group also presented lower risks of all--cause death, cardiac death, stroke, and definite/ /probable ST than those in DAPT ≤ 1 year group. Moreover, the risk of clinically relevant bleeding did not statistically differ between the extended DAPT and shortened DAPT groups (Fig. 4A, **Suppl. Fig. S1, Suppl. Table S2**).

In contrast, no statistically difference was found between DAPT > 1 year and DAPT ≤ 1 year groups in terms of the primary endpoint of MACCE at 2.4 years (1.3% vs. 2.0%; adjusted HR 0.736, 95% CI 0.374–1.449) in individuals with normal Lp(a) levels. Patients in DAPT > 1 year group had lower risks of all-cause mortality, and definite/ /probable ST compared with those in DAPT ≤ 1 year group. The risk of BARC type 2, 3 or 5 bleeding in extended DAPT group did not significantly differ from that in shortened DAPT group (Fig. 4B, **Suppl. Fig. S1, Suppl. Table S2**).

In IPTW analysis, all the candidate variables were well balanced between the DAPT ≤ 1 year and DAPT > 1 year groups in both the patients with normal and elevated Lp(a) levels (Fig. 3). Consistent with the results of multivariable Cox regression analysis, it suggested lower risks of MACCE and all-cause death in DAPT > 1 year group than that in DAPT ≤ 1 year group in individuals with elevated Lp(a) levels (Fig. 4A). In individuals with normal Lp(a) levels, the risk of MACCE did not statistically differ between DAPT > 1 year and DAPT ≤ 1 year groups, while extended DAPT was associated with lower risk of all-cause death and definite/probable ST in these patients (Fig. 4B).

Table 1. Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
Age [years]	58 (50–65)	58 (50–65)	0.775	58 (50–65)	58 (50–64)	0.779
Male	755 (81.1%)	1674 (82.7%)	0.275	352 (80.5%)	750 (77.6%)	0.219
Body mass index [kg/m^2]	26.0 (23.9–27.8)	26.0 (24.0–28.0)	0.484	25.5 (23.5–27.7)	25.5 (23.7–27.7)	0.490
Current smoker	557 (59.8%)	1275 (63.0%)	0.096	275 (62.9%)	557 (57.7%)	0.063
Diabetes mellitus	376 (40.4%)	833 (41.2%)	0.685	177 (40.5%)	361 (37.4%)	0.264
Hypertension	583 (62.6%)	1240 (61.3%)	0.491	273 (62.5%)	622 (64.4%)	0.489
Dyslipidemia	605 (65.0%)	1334 (65.9%)	0.611	265 (60.6%)	664 (68.7%)	**0.003**
Previous myocardial infarction	116 (12.5%)	283 (14.0%)	0.259	59 (13.5%)	121 (12.5%)	0.613
Previous PCI	169 (18.2%)	395 (19.5%)	0.378	92 (21.1%)	204 (21.1%)	0.978
Previous CABG	31 (3.3%)	69 (3.4%)	0.910	20 (4.6%)	40 (4.1%)	0.709
Previous stroke	77 (8.3%)	197 (9.7%)	0.202	49 (11.2%)	94 (9.7%)	0.396
Peripheral vascular disease	14 (1.5%)	50 (2.5%)	0.093	7 (1.6%)	21 (2.2%)	0.478
Chronic kidney disease	85 (9.1%)	214 (10.6%)	0.226	35 (8.0%)	95 (9.8%)	0.275
COPD	23 (2.5%)	48 (2.4%)	0.872	15 (3.4%)	19 (2.0%)	0.098
LVEF [%]	64 (60–68)	64 (60–68)	0.551	64 (60–68)	64 (60–68)	0.652
LVEF < 50%	40 (4.4%)	79 (4.0%)	0.590	17 (4.0%)	34 (3.7%)	0.763
Systolic blood pressure [mmHg]	125 (120–140)	125 (120–138)	0.812	120 (115–137)	120 (115–140)	0.466
Laboratory data:						
WBC [10^3/μL]	6.51 (5.55–7.79)	6.55 (5.51–7.79)	0.968	6.46 (5.51–7.66)	6.64 (5.61–7.94)	0.167
Hemoglobin [g/L]	145 (135–155)	146 (136–155)	0.410	145 (135–156)	145 (135–154)	0.772
TC [mmol/L]	3.94 (3.38–4.71)	3.96 (3.36–4.69)	0.772	4.14 (3.55–4.89)	4.22 (3.60–4.97)	0.171
LDL-C [mmol/L]	2.26 (1.79–2.89)	2.27 (1.79–2.88)	0.842	2.47 (1.98–3.09)	2.53(2.00–3.20)	0.315
HDL-C [mmol/L]	0.99 (0.85–1.16)	0.96 (0.81–1.15)	**0.016**	1.02 (0.86–1.17)	1.01 (0.86–1.23)	0.729
HbA1c [%]	6.2 (5.8–6.8)	6.2 (5.8–6.9)	0.670	6.1 (5.7–6.8)	6.2 (5.8–6.9)	0.252
Lp(a) [mg/dL]	10.1 (4.9–17.9)	10.5 (5.2–17.7)	0.400	54.0 (39.1–81.5)	53.8 (39.5–81.2)	0.654
Radial artery access	883 (94.8%)	1871 (92.5%)	**0.018**	411 (94.1%)	893 (92.4%)	0.276
Multivessel disease	639 (68.6%)	1450 (71.7%)	0.092	315 (72.1%)	721 (74.6%)	0.313

→

Table 1 (cont.). Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
SYNTAX score	9 (6–15)	9 (5–15)	0.643	10 (7–17)	10 (6–16)	0.203
SYNTAX score > 22	75 (8.2%)	168 (8.5%)	0.803	45 (10.7%)	90 (9.6%)	0.549
Total lesion length [mm]	28 (18–47)	30 (18–48)	0.282	30 (20–50)	32 (20–48)	0.962
Target lesion morphology:						
Bifurcation lesion	186 (20.0%)	371 (18.3%)	0.290	87 (19.9%)	187 (19.4%)	0.810
2-stent technique	39 (4.2%)	83 (4.1%)	0.913	18 (4.1%)	41 (4.2%)	0.914
Chronic total occlusion	134 (14.4%)	314 (15.5%)	0.427	73 (16.7%)	165 (17.1%)	0.862
In-stent restenosis	36 (3.9%)	90 (4.4%)	0.467	19 (4.3%)	42 (4.3%)	1.000
Severe calcification	16 (1.7%)	60 (3.0%)	**0.047**	7 (1.6%)	32 (3.3%)	0.071
Angulation > 45 degrees	104 (11.2%)	193 (9.5%)	0.171	47 (10.8%)	96 (9.9%)	0.639
Type B2 or C lesion	691 (74.2%)	1484 (73.4%)	0.620	341 (78.0%)	736 (76.2%)	0.449
No. vessels treated	1 (1–1)	1 (1–1)	0.161	1 (1–2)	1 (1–2)	0.780
No. lesions treated	1 (1–2)	1 (1–2)	0.421	1 (1–2)	1 (1–2)	0.944
No. lesions treated ≥ 3	58 (6.2%)	131 (6.5%)	0.800	27 (6.2%)	60 (6.2%)	0.981
Drug-eluting stent number	2 (1–2)	2 (1–2)	0.116	2 (1–2)	2 (1–2)	0.432
Drug-eluting stent number ≥ 3	184 (19.8%)	415 (20.5%)	0.637	92 (21.1%)	203 (21.0%)	0.987
Use of EES/ZES	513 (55.1%)	1153 (57.0%)	0.335	250 (57.2%)	534 (55.3%)	0.500
Minimum stent diameter [mm]	3.00 (2.50–3.50)	3.00 (2.50–3.50)	0.193	3.00 (2.50–3.50)	2.75 (2.50–3.00)	0.075
Total stent length [mm]	33 (23–51)	33 (21–52)	0.444	34 (23–54)	36 (23–52)	0.923
DAPT score	2 (1–3)	2 (1–3)	0.057	2 (1–3)	2 (1–3)	0.205
DAPT score ≥ 2	511 (54.9%)	1187 (58.7%)	0.053	262 (60.0%)	562 (58.2%)	0.531
Medications at discharge:						
ASA	931 (100%)	2023 (100%)	NA	437 (100%)	966 (100%)	NA
$P2Y_{12}$ receptor inhibitor	931 (100%)	2023 (100%)	NA	437 (100%)	966 (100%)	NA
Oral anticoagulant	4 (0.6%)	3 (0.2%)	0.241	0 (0%)	1 (0.2%)	1.000
Beta-blockers	811 (87.1%)	1780 (88.0%)	0.500	394 (90.2%)	864 (89.4%)	0.682
Statins	889 (95.5%)	1948 (96.3%)	0.298	423 (96.8%)	925 (95.8%)	0.352
Calcium channel blockers	459 (49.3%)	1029 (50.9%)	0.430	229 (52.4%)	510 (52.8%)	0.892

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Table 1 (cont.). Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
Antiplatelet drugs at 6 months:	N = 931	N = 2023		N = 437	N = 966	
ASA	919 (98.7%)	2023 (100%)	< 0.001	432 (98.9%)	966 (100%)	**0.003**
$P2Y_{12}$ receptor inhibitor	915 (98.3%)	2023 (100%)	**< 0.001**	432 (98.9%)	966 (100%)	**0.003**
Antiplatelet drugs at 12 months:	N = 931	N = 2023		N = 437	N = 966	
ASA	887 (95.3%)	2023 (100%)	**< 0.001**	423 (96.8%)	966 (100%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	854 (91.7%)	2023 (100%)	**< 0.001**	398 (91.1%)	966 (100%)	**< 0.001**
Antiplatelet drugs at 18 months:	N = 931	N = 2023		N = 437	N = 965	
ASA	846 (90.9%)	2015 (99.6%)	**< 0.001**	408 (93.4%)	959 (99.4%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	23 (2.5%)	1829 (90.4%)	**< 0.001**	15 (3.4%)	861 (89.2%)	**< 0.001**
Antiplatelet drugs at 24 months:	N = 930	N = 2014		N = 437	N = 962	
ASA	841 (90.4%)	1973 (98.0%)	**< 0.001**	407 (93.1%)	943 (98.0%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	19 (2.0%)	840 (41.7%)	**< 0.001**	13 (3.0%)	408 (42.4%)	**< 0.001**
Antiplatelet drugs at 30 months:	N = 239	N = 779		N = 104	N = 367	
ASA	206 (86.2%)	763 (97.9%)	**0.003**	89 (85.6%)	361 (98.4%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	5 (2.1%)	230 (29.5%)	< 0.001	4 (3.8%)	104 (28.3%)	**< 0.001**
DAPT time [days]	349 ± 62	661 ± 164	**< 0.001**	348 ± 60	661 ± 163	**< 0.001**
	365 (365, 365)	548 (548, 802)		365 (365, 365)	548 (548, 790)	

ASA — acetylsalicylic acid; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; DAPT — dual antiplatelet therapy; EES — everolimus-eluting stent; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; TC — total cholesterol; WBC — white blood cell; ZES — zotarolimus-eluting stent

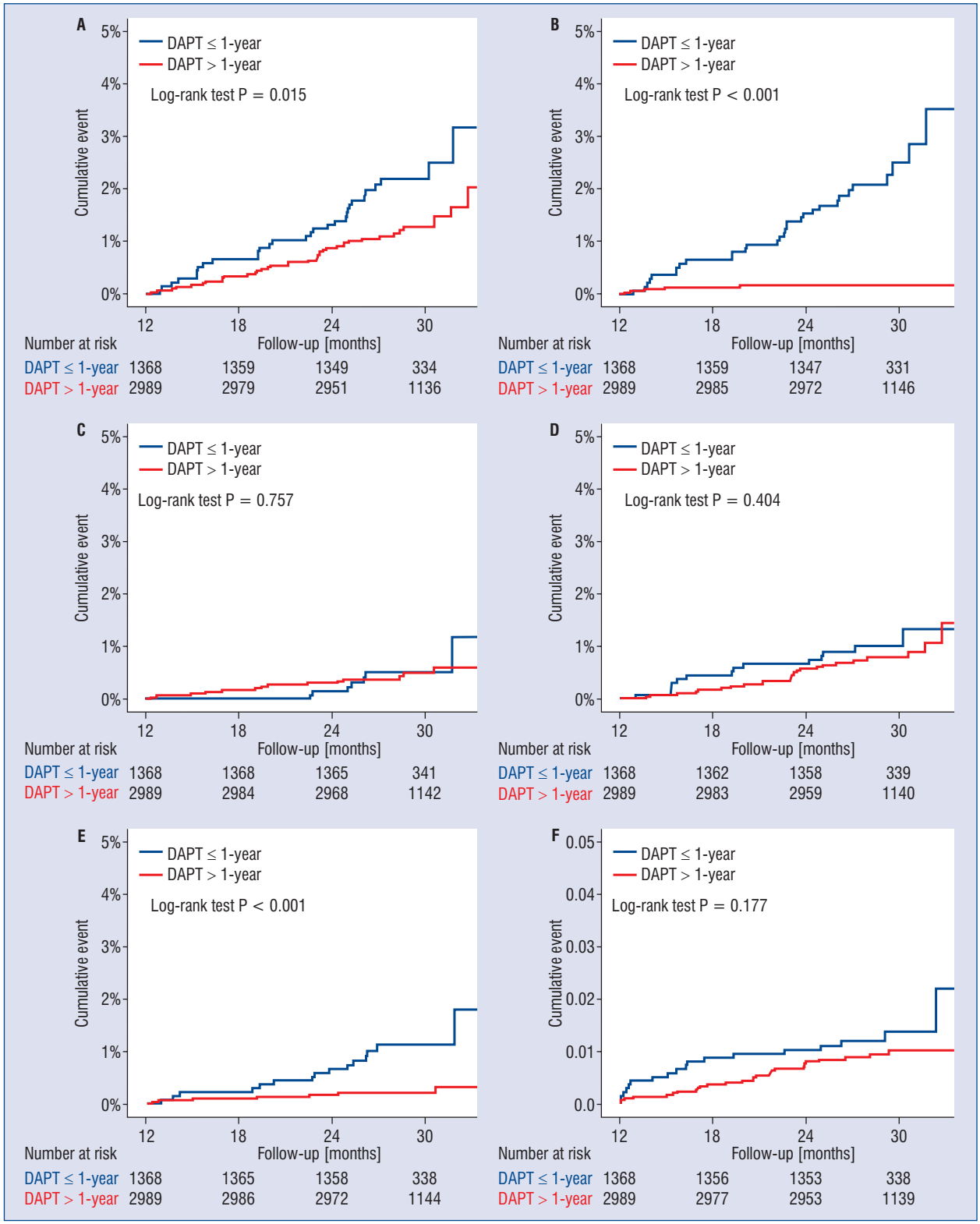

Figure 2. Kaplan–Meier curves for 2.4-year clinical outcomes according to dual antiplatelet therapy (DAPT) duration in overall population; **A.** Cardiac death/MI/stroke; **B.** All-cause death; **C.** MI; **D.** Stroke; **E.** Definite/probable ST; **F.** BARC type 2, 3 or 5 bleeding; BARC — Bleeding Academic Research Consortium; MI — myocardial infarction; ST — stent thrombosis.

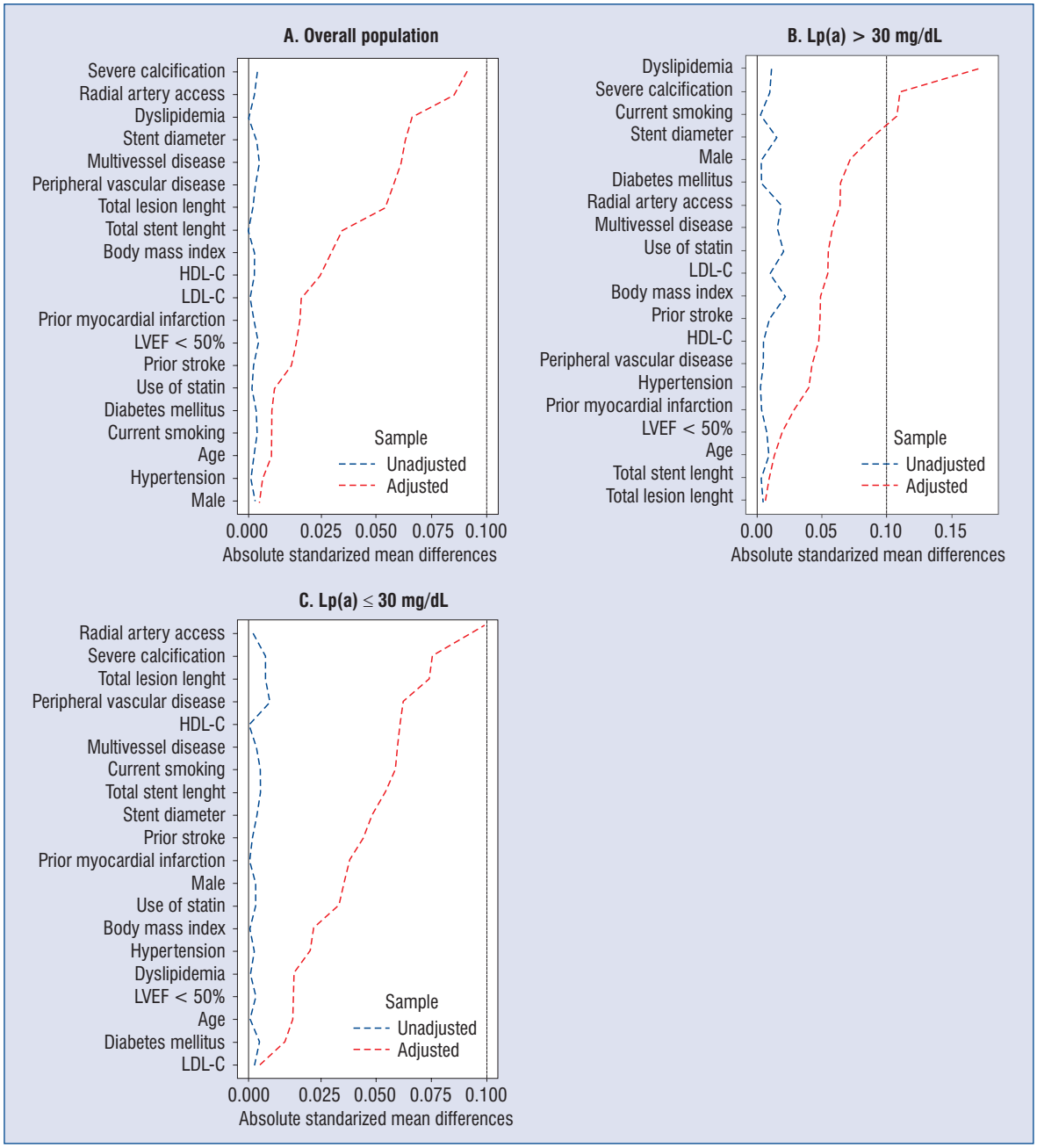

Figure 3. Absolute standard difference before and after inverse probability of treatment weighting analysis between the dual antiplatelet therapy (DAPT) > 1 year and DAPT ≤ 1 year groups in (**A**) overall population (**B**) patients with lipoprotein(a) [Lp(a)] levels > 30 mg/dL and (**C**) patients with Lp(a) levels ≤ 30 mg/dL, respectively; HDL-C — high--density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction.

Discussion

The present study is the first to specifically evaluate the effect of Lp(a) concentrations on the clinical outcomes of extended DAPT among a cohort of consecutive ACS patients after PCI. The major findings are as follows: (1) Extended DAPT contributed to the reduction of cardiovascular events without statistically increasing clinically relevant bleeding events in patients with ACS after PCI with DES; (2) The clinical benefit of extended DAPT was more pronounced in individuals with Lp(a) > 30 mg/dL, whereas in individuals with Lp(a) ≤ 30 mg/dL, extended DAPT did not show significant evidence of benefit in reducing the composite endpoint of MACCE.

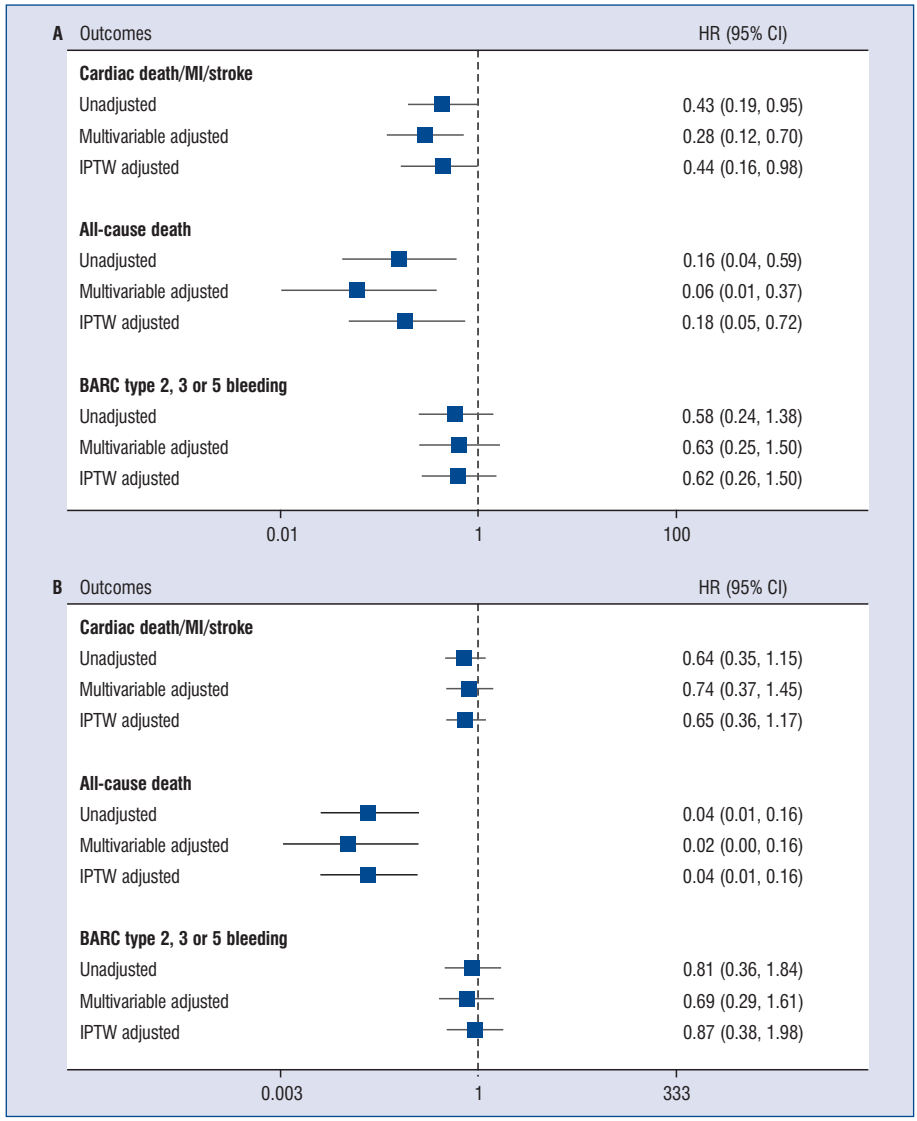

Figure 4. Unadjusted and adjusted association between dual antiplatelet therapy duration and main clinical outcomes in patients with (**A**) lipoprotein(a) [Lp(a)] levels > 30 mg/dL and (**B**) Lp(a) levels ≤ 30 mg/dL, respectively; BARC — Bleeding Academic Research Consortium; CI — confidence interval; IPTW — inverse probability of treatment weighting; HR — hazard ratio; MI — myocardial infarction.

Lipoprotein(a) is a lipoprotein particle formed by adding a carbohydrate-rich protein, i.e., apo(a), to apoB-100 on LDL particles via disulfide bonds. Although not fully understood, Lp(a) potentially contributes to cardiovascular disease through proatherogenic effects of its LDL-like moiety, prothrombotic effects through its plasminogen--like apo(a), and proinflammatory effects of its oxidized phospholipid content. Actually, there was overwhelming evidence from epidemiology and genetics that Lp(a) was an independent predictor of cardiovascular disease [1, 2]. For example, a large-scare meta-analysis including 126,634 patients confirmed a strong relationship between high Lp(a) levels and the incidence of CAD and stroke [4]. Furthermore, several studies demonstrated that high Lp(a) levels were associated with an increased risk of long-term recurrent cardiovascular events in patients undergoing PCI or with ACS. Based on data of 10,059 patients undergoing PCI (including 5923 ACS patients), it was found that Lp(a) > 30 mg/dL was positively related to higher risk of MACCE (death, MI, stroke or unplanned revascularization) at 2.4-year follow-up [7]. Konishi et al. [8] reported that elevated Lp(a) levels were significantly associated with higher incidence of

4.7-year cardiac death or ACS for diabetic patients who received PCI. Moreover, a study with 988 ACS patients who achieved target lipid levels suggested that Lp(a) was positively related to the composite endpoint of death, MI, or target vessel revascularization during 29-month follow-up [9].

One potential therapeutic approach to reduce the Lp(a)-associated poor prognosis is to reduce Lp(a) concentrations. Nevertheless, traditional lipid-lowering agents have little or moderate effect on reducing Lp(a) levels. Currently, there are no approved pharmacotherapies specifically targeting high Lp(a) concentrations. A post hoc analysis of the ODYSSEY OUTCOMES trial found a clinical benefit of PCSK9 inhibitors in ACS patients, however, the clinical benefit of PCSK9 inhibitors by reducing Lp(a) levels was very low [23]. Although a hepatocyte directed antisense oligonucleotides, APO(a)-L_{Rx}, could largely reduce the Lp(a) levels in patients with cardiovascular disease, whether it will provide clinical benefit remains to be seen [24]. Indeed, previous studies speculated that a reduction of 50–100 mg/dL in Lp(a) may be required to obtain significant clinical benefit [25–27]. However, many large-scale studies revealed that the incidences of cardiovascular events in participants with Lp(a) levels ranged from 30 mg/dL to 50 mg/dL are also very high, and these patients may not benefit from Lp(a)-lowering therapies [1, 4, 7, 18].

Due to the high degree of homology between apo(a) and plasminogen, Lp(a) potentiates thrombosis through inhibiting plasminogen activation and fibrin degradation, and promoting endothelial plasminogen activator inhibitor expression, tissue factor pathway inhibitor activity, and platelet reactivity [2]. The ASPREE trial enrolled 12,815 individuals without prior cardiovascular disease, and it reported that rs3798220-C carrier status or high LPA-GRS was associated with increased risk of cardiovascular events in the placebo group but not in the ASA group. Moreover, in the rs3798220-C and high LPA-GRS subgroups, the overall benefit of ASA may outweigh harm related to major bleeding, whereas the reduction of cardiovascular events and the increase of clinically significant bleeding was equal in overall participants [11]. Similarly, in the Women's Health Study with women ≥ 45 years old, although the overall trial was negative, women with elevated Lp(a) levels benefited from ASA use, which suggested the risk could be modified by antiplatelet therapy (age-adjusted HR 0.44, 95% CI 0.20–0.94) [12]. In this setting, it was hypothesized herein, that enhanced antithrombotic therapy or extended DAPT after PCI may be beneficial for ACS patients with high Lp(a) levels. Therefore, the relative efficacy was compared and safety of extended DAPT (> 1 year) versus shortened DAPT (≤ 1 year) in ACS patients with elevated Lp(a) levels and normal Lp(a) levels, respectively.

The present study revealed that extended DAPT (up to 30 months) could reduce the risks of MACCE and all-cause death without statistically increasing clinically relevant bleeding for ACS patients with elevated Lp(a) levels after PCI. However, extended DAPT was not significantly associated with reduced incidence of the composite cardiovascular events for patients with normal Lp(a) levels, although the risks of all-cause death and definite/ /probable ST were lower in extended DAPT group than that in shortened DAPT group. Similarly, the author's previous study with 3,201 stable CAD patients, the beneficial effect of extended DAPT was well established in patients with elevated Lp(a) levels, whereas extended DAPT tended to increase clinically relevant bleeding without reducing ischemic events in those with normal Lp(a) levels [16]. Notably, unlike the previous study, the present study did not find that extended DAPT increased the risk of clinically relevant bleeding in ACS patients with normal Lp(a) levels. This suggests that in this population, although the benefit of prolonged DAPT is not as great as that in ACS patients with elevated Lp(a) levels, it at least does not cause harm. Different from stable CAD patients who have not sustained a previous ischemic event, a heightened predisposition to thrombotic events may persist for years for patients with ACS [28, 29]. Therefore, ACS patients may be more likely to benefit from extended DAPT than those with stable CAD, and Lp(a) levels should be an important consideration in determining the DAPT duration after PCI for ACS patients.

Limitations of the study

There were several limitations in this study. First, this is a single-center, observational study, and the confounders might be complex. Although the confounding factors were adjusted through multivariable-adjusted analysis and IPTW analysis, it was not possible to control the unmeasured confounders and eliminate the selection bias. Second, the composite endpoint of MACCE did not reach statistical significance in ACS patients with normal Lp(a) levels, possibly due to the relatively small sample size and low incidence of ischemic events. It is well known that relatively low event rates can lead to an increased likelihood of overfitting. Third, although the clinical benefit of extended DAPT

was confirmed in ACS patients with elevated Lp(a) levels, the current findings were derived from subgroup analysis of the cohort study and the results should be interpreted as hypothesis generating. Fourth, clopidogrel, instead of ticagrelor or prasugrel was predominantly used as a $P2Y_{12}$ inhibitor for DAPT regimen (only 5 patients received ticagrelor), thus the clinical impact of extended DAPT with ASA plus a more potent $P2Y_{12}$ inhibitor in ACS patients with different Lp(a) concentrations is unclear. Given that current guidelines recommend ticagrelor or prasugrel in ACS, further well-designed, large-scale, randomized trials with new $P2Y_{12}$ inhibitors are needed. Last, the conclusions drawn from this study may not be generalized to those other than Asian ethnicities.

Conclusions

This study firstly demonstrated that extended DAPT (> 1 year) was statistically associated with lower risk of ischemic events in ACS patients with elevated Lp(a) levels after DES implantation, whereas this association was not found in individuals with normal Lp(a) levels. Further well-designed, large-scale, randomized trials are needed to confirm these findings.

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