Journal of the American Heart Association

ORIGINAL RESEARCH

How Do Lipoprotein(a) Concentrations Affect Clinical Outcomes for Patients With Stable Coronary Artery Disease Who Underwent Different Dual Antiplatelet Therapy After Percutaneous Coronary Intervention?

Kongyong Cui, MD; Dong Yin, MD; Chenggang Zhu, MD; Weihua Song, MD; Hongjian Wang, MD; Lei Jia, MD; Rui Zhang, MD; Haoyu Wang, MD; Zhongxing Cai, MD; Lei Feng, MD; Kefei Dou, MD

BACKGROUND: Lp(a) (lipoprotein[a]) plays an important role in predicting cardiovascular events in patients with coronary artery disease through its proatherogenic and prothrombotic effects. We hypothesized that prolonged dual antiplatelet therapy (DAPT) might be beneficial for patients undergoing percutaneous coronary intervention who had elevated Lp(a) levels. This study aimed to evaluate the effect of Lp(a) on the efficacy and safety of prolonged DAPT versus shortened DAPT in stable patients with coronary artery disease who were treated with a drug-eluting stent.

METHODS AND RESULTS: We selected 3201 stable patients with CAD from the prospective Fuwai Percutaneous Coronary Intervention Registry, of which 2124 patients had Lp(a) ≤30 mg/dL, and 1077 patients had Lp(a) >30 mg/dL. Patients were divided into 4 groups according to Lp(a) levels and the duration of DAPT therapy (≤1 year versus >1 year). The primary end point was major adverse cardiovascular and cerebrovascular event, defined as a composite of all-cause death, myocardial infarction, or stroke. The median follow-up time was 2.5 years. Among patients with elevated Lp(a) levels, DAPT >1 year presented lower risk of major adverse cardiovascular and cerebrovascular event and definite/probable stent thrombosis compared with DAPT ≤1 year. In contrast, in patients with normal Lp(a) levels, the risks of major adverse cardiovascular and cerebrovascular event and definite/probable stent thrombosis were not significantly different between the DAPT >1 year and DAPT ≤1 year groups. Prolonged DAPT had 2.4-times higher risk of clinically relevant bleeding than shortened DAPT in patients with normal Lp(a) levels, although without statistical difference.

CONCLUSIONS: In stable patients with coronary artery disease, who underwent percutaneous coronary intervention with a drug-eluting stent, prolonged DAPT was associated with reduced risk of cardiovascular events among those with elevated Lp(a) levels, whereas it did not show statistically significant evidence of benefit for reducing ischemic events and tended to increase clinically relevant bleeding among those with normal Lp(a) levels.

Key Words: clinical outcome ■ coronary artery disease ■ drug-eluting stent ■ dual antiplatelet therapy ■ lipoprotein(a) ■ percutaneous coronary intervention

Correspondence to: Lei Feng, MD, or Kefei Dou, MD, Cardiometabolic Medicine Center, Department of Cardiology, 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. Email: fenglei0721@163.com, drdoukefei@126.com

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023578

For Sources of Funding and Disclosures, see page 14.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The effect of prolonged dual antiplatelet therapy in patients who underwent percutaneous coronary intervention with a drug-eluting stent has never been evaluated.
- This cohort study first suggested that prolonged dual antiplatelet therapy was associated with reduced ischemic events in patients with elevated Lp(a) (lipoprotein[a]) levels but not in those with normal Lp(a) levels.

What Are the Clinical Implications?

- This study provides convincing evidence for the role of prolonged dual antiplatelet therapy for stable patients with coronary artery disease with elevated Lp(a) levels who underwent percutaneous coronary intervention with a drug-eluting stent.
- Lp(a) levels might be an important consideration when deciding upon the duration of dual antiplatelet therapy for stable patients with coronary artery disease undergoing percutaneous coronary intervention with a drug-eluting stent.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
DES	drug-eluting stent
IPTW	inverse probability of treatment weighting
Lp(a)	lipoprotein(a)
MACCE	major adverse cardiovascular and cerebrovascular event
ST	stent thrombosis

Elevated Lp(a) (lipoprotein[a]) is one of the most common genetic lipid disorders, affecting 20% to 30% of the population worldwide.[1] Over the past decade, Lp(a) has been shown to be an independent and causal risk factor for cardiovascular disease.[2–8] Moreover, increasing evidence supports that Lp(a) levels play an important role in predicting subsequent ischemic events in patients with coronary artery disease (CAD).[9–13] In a prospective, multicenter study with 4078 stable patients with CAD undergoing percutaneous coronary intervention (PCI), Liu et al reported that high Lp(a) levels were associated with a poor prognosis at a mean follow-up of 4.9 years.[12] Nevertheless, there are no approved pharmacologic therapies that are specifically aimed at lowering Lp(a) levels. Although a novel therapeutic agent, hepatocyte-directed antisense oligonucleotide apoA-L_{Rx} (apolipoprotein A-L_{Rx}), has showed an average of 80% reduction in Lp(a) levels, the impact of this Lp(a)-lowering drug on major cardiovascular events in patients with CAD remains unknown.[14]

Dual antiplatelet therapy (DAPT) is the cornerstone of pharmacological treatment for preventing thrombotic complications after PCI. Given that Lp(a) has a prothrombotic effect through its inactive, plasminogen-like protease domain on apoA (apolipoprotein A),[15,16] prolonged DAPT may have a beneficial effect on reducing ischemic events in patients with CAD undergoing PCI who have elevated Lp(a) levels. However, the relative benefit of prolonged DAPT in this population has never been evaluated. Therefore, we conducted this study to assess the effect of Lp(a) levels on the efficacy and safety of prolonged DAPT (>1 year) versus shortened DAPT (≤1 year) in stable patients with CAD who underwent PCI with a drug-eluting stent (DES) in a large and contemporary PCI registry.

METHODS

We will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This was an analysis of a single center, prospective study, and the study design has been previously described.[17,18] Patients with stable CAD who underwent PCI with DES implantation at Fuwai Hospital, National Center for Cardiovascular Diseases, between January 2013 and December 2013 were selected. Stable CAD refers to patients with CAD who are clinically stable (ie, who are not in an unstable phase such as an acute coronary syndrome [ACS]).[19] This study was performed according to the principles of the Declaration of Helsinki, and ethics approval was obtained from the ethical committee of Fuwai Hospital. All patients provided written informed consent before enrollment. For the present analysis, patients with missing Lp(a) data, ACS, or infectious inflammatory disease or malignant tumor were not included. We excluded patients who did not receive DAPT, did not use a DES, or experienced major adverse events (death, myocardial infarction [MI], stent thrombosis [ST], stroke, repeat revascularization, or Bleeding Academic Research Consortium type 2, 3, or 5 bleeding) within the 1-year follow-up. There were 3201 patients selected for the final analysis.

Study Procedures and Biochemical Analysis

All procedures and medical therapies were performed according to guidelines' recommendation and operators' discretion. Detailed information on procedures has been previously described.[20] After fasting for ≥12 hours before PCI, blood samples for measurement of Lp(a) and other biomarkers were obtained, and the test was conducted through the clinical chemistry department in our hospital. Lp(a) was measured by immunoturbidimetry method (LASAY Lp[a] auto; SHIMA Laboratories, Tokyo, Japan) with a normal range 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%.[12] Low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol were analyzed using an automated biochemical analyzer (Hitachi 7150; Hitachi, Tokyo, Japan), and glycosylated hemoglobin was tested with the Tosoh Automated Glycohemoglobin Analyzer (HLC-723G8; Tosoh, Tokyo, Japan).

Previous meta-analyses and the current guidelines for the management of dyslipidemia from China and Canada suggested that the relationship between Lp(a) and cardiovascular risk inflects at a concentration of 30 mg/dL.[5,11,21,22] Therefore, we used a cutoff of >30 mg/dL to assign abnormal Lp(a) levels. Patients were divided into 4 groups according to Lp(a) levels (≤30 mg/dL versus >30 mg/dL) and the duration of DAPT therapy of DAPT ≤1 year versus DAPT >1 year.

Follow-Up and End Points

Demographics, cardiovascular risk factors, clinical parameters, laboratory data, and angiographic and procedural details were extracted from our dedicated PCI registry by independent research personnel. After the index PCI, patients were followed up at 1, 6, and 12 months and annually thereafter. Data for end points were collected from medical records, clinical visits, and telephone interviews by trained investigators who were blind to the clinical data. To record ≥2-year follow-up information for each patient, we extended the follow-up period to January 31, 2016. Adherence to antiplatelet medication was routinely assessed at each time of follow-up, and the status of antiplatelet therapy (ie, aspirin and clopidogrel) was collected by dedicated questionnaires and the electronic prescribing system.

The primary end point was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of death, nonfatal MI, or stroke. Secondary end points consisted of the individual components of the primary end point, cardiac death, definite or probable ST, and Bleeding Academic Research Consortium type 2, ,3 or 5 bleeding. All deaths were considered to be cardiac-related unless a noncardiac origin was documented. MI was defined in compliance with the third universal definition of MI, with periprocedural MI not included.[23] Stroke was defined as new focal neurological deficit lasting >24 hours based on imaging evidence. Definite or probable ST was adjudicated on the basis of the Academic Research Consortium criteria.[24] Bleeding events were categorized on the basis of the Bleeding Academic Research Consortium classifications.[25] All events were carefully verified and adjudicated by independent clinicians.

Statistical Analysis

Continuous variables were expressed as mean± standard deviation or median (interquartile range), and categorical variables were expressed as frequency (percentage). Differences in various characteristics were compared using the Student *t* test, Wilcoxon rank sum test, Pearson χ^2 test, or Fisher exact test, as appropriate. Cumulative incidence of clinical events was estimated using Kaplan-Meier curves, and differences were assessed with log-rank tests. Single-variable and multivariable Cox regression analyses, as well as inverse probability of treatment weighting (IPTW) analysis, were performed to calculate hazard ratios (HRs) and 95% CIs.

An IPTW analysis was also conducted to adjust for differences in baseline characteristics for drawing inferences about the relative efficacy and safety of DAPT >1 year versus DAPT ≤1 year in each subgroup of patients (ie, patients with elevated Lp[a] levels [>30 mg/dL] and those with normal Lp[a] levels [≤30 mg/dL]. A propensity score was developed using a nonparsimonious multivariable logistic regression model and considering DAPT time (DAPT >1 year versus DAPT ≤1 year) as the dependent variable. Covariates used for the propensity score model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous PCI, previous stroke, peripheral vascular disease, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein cholesterol, total lesion length, type B2 or C lesion, chronic total occlusion, bifurcation lesion, number of lesions treated, stent number, use of everolimus- or zotarolimus-eluting stent, and use of a β-blocker and statin at discharge. The detailed methods of IPTW analysis were previously described.[18] All statistical analyses were conducted with SPSS version 23.0 (IBM, Armonk, NY) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Among the 3201 stable patients with CAD who underwent PCI, 2124 had normal Lp(a) concentrations,

of which 608 received DAPT ≤1 year and 1516 received DAPT >1 year. Among the 1077 patients who had elevated Lp(a) levels, 292 received DAPT ≤1 year and 785 received DAPT >1 year (Figure 1). The median follow-up period was 2.5 years (2.2–2.6 years). Compared with patients who received ≤1 year DAPT, patients who received >1 year DAPT had longer lesion length and more bifurcation lesions, and they received more 2-stent techniques and more stent implantations with longer length during the intervention (Table 1). As shown in Table S1, compared with patients who had normal Lp(a) levels, those with elevated Lp(a) levels were older, less likely to be men or a current smoker, and had longer lesion length and more type B2 or C lesions. Subsequently, these patients used more stents with smaller diameter and longer total length during PCI. In patients with normal Lp(a) levels, those who received DAPT >1 year had longer lesion length, more bifurcation lesion, and received more 2-stent techniques, and more stents implantations with longer total lesion length than those who received DAPT ≤1 year. In patients with elevated Lp(a) concentrations, more everolimus- or zotarolimus-eluting stents were used in those who received DAPT >1 year than those who received DAPT ≤1 year (Table 2).

DAPT Duration and 2.5-Year Clinical Outcomes

As shown in Table 3 and Figure 2, patients who received DAPT >1 year had lower risks of MACCE (1.5% versus 2.6%; adjusted HR, 0.536 [95% CI, 0.313–0.915]), all-cause death (0.1% versus 1.8%; adjusted HR, 0.045 [95% CI, 0.010–0.198]), and definite/probable ST (0.2% versus 1.0%; adjusted HR, 0.150 [95% CI, 0.046–0.498]) than those who received DAPT ≤1 year. All the candidate variables were well balanced between the DAPT ≤1 year and DAPT >1 year groups

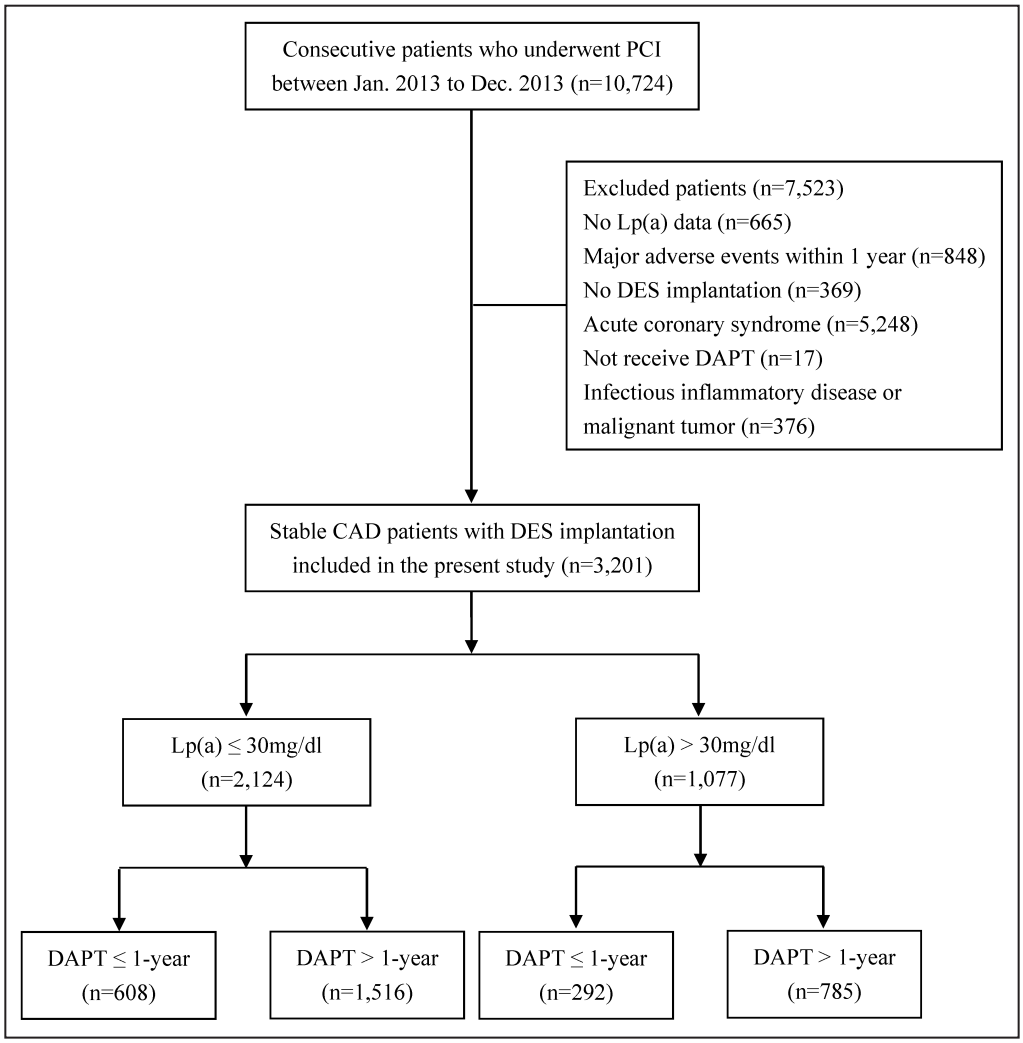

Figure 1. Flowchart of the study.
CAD indicates coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Lp(a), lipoprotein(a); and PCI, percutaneous coronary intervention.

Table 1. Baseline Patient, Angiographic, and Procedural Characteristics According to DAPT Duration

Variable	DAPT ≤1 y, n=900	DAPT >1 y, n=2301	*P* value
Age, y	58 (50–64)	58 (50–65)	0.433
Men, n (%)	723 (80.3)	1860 (80.8)	0.747
Body mass index, kg/m^2	26.0 (24.1–28.0)	26.0 (24.0–27.8)	0.357
Current smoker, n (%)	520 (57.8)	1288 (56.0)	0.355
Diabetes, n (%)	282 (31.3)	701 (30.5)	0.632
Hypertension, n (%)	567 (63.0)	1493 (64.9)	0.317
Dyslipidemia, n (%)	613 (68.1)	1605 (69.8)	0.365
Previous myocardial infarction, n (%)	238 (26.4)	674 (29.3)	0.109
Previous PCI, n (%)	264 (29.3)	656 (28.5)	0.643
Previous CABG, n (%)	29 (3.2)	108 (4.7)	0.064
Previous stroke, n (%)	98 (10.9)	228 (9.9)	0.410
Peripheral vascular disease, n (%)	23 (2.6)	83 (3.6)	0.135
Chronic kidney disease, n (%)	74 (8.2)	227 (9.9)	0.152
COPD, n (%)	14 (1.6)	53 (2.3)	0.184
LVEF, %	65 (60–68)	64 (60–68)	0.094
LVEF <50%, n (%)	28 (3.2)	96 (4.3)	0.162
Systolic blood pressure, mm Hg	125 (120–140)	126 (120–140)	0.832
Laboratory data			
WBC, 10^3/μL	6.50 (5.43–7.50)	6.33 (5.40–7.45)	0.138
Hemoglobin, g/L	146 (136–155)	145 (135–155)	0.801
Total cholesterol, mmol/L	3.97 (3.46–4.82)	4.00 (3.35–4.76)	0.432
LDL-C, mmol/L	2.28 (1.88–3.0)	2.31 (1.80–2.94)	0.265
HDL-C, mmol/L	1.02 (0.87–1.17)	1.01 (0.86–1.18)	0.347
HbA1c, %	6.2 (5.8–6.9)	6.2 (5.9–6.9)	0.261
Lp(a), mg/dL	17.1 (7.0–38.0)	16.8 (7.2–40.0)	0.592
Radial artery access, n (%)	758 (91.8)	1935 (91.3)	0.667
Multivessel disease, n (%)	673 (74.8)	1772 (77.0)	0.181
SYNTAX score	10 (6–16)	10 (7–17)	0.110
SYNTAX score >22, n (%)	93 (10.7)	260 (11.7)	0.407
Total lesion length, mm	32 (20–50)	34 (20–55)	0.032
Target lesion morphology			
Bifurcation lesion, n (%)	167 (18.6)	528 (22.9)	0.007
2-stent technique, n (%)	26 (2.9)	126 (5.5)	0.002
Chronic total occlusion, n (%)	164 (18.2)	428 (18.6)	0.804
In-stent restenosis, n (%)	43 (4.8)	110 (4.8)	0.997
Severe calcification, n (%)	34 (3.8)	82 (3.6)	0.771
Angulation >45°, n (%)	94 (10.4)	276 (12.0)	0.217
Type B2 or C lesion, n (%)	685 (76.1)	1818 (79.0)	0.074
No. vessels treated	1 (1–2)	1 (1–1)	0.796
No. lesions treated	1 (1–2)	1 (1–2)	0.590
No. lesions treated ≥3, n (%)	64 (7.1)	168 (7.3)	0.852
Drug-eluting stent number	2 (1–2)	2 (1–3)	0.002
Drug-eluting stent number ≥3, n (%)	203 (22.6)	614 (26.7)	0.016
Type of drug-eluting stent			0.038
PES/SES, n (%)	426 (47.3)	996 (43.3)	
EES/ZES, n (%)	474 (52.7)	1305 (56.7)	
Minimum stent diameter, mm	2.75 (2.50–3.00)	2.75 (2.50–3.00)	0.808

(*Continued*)

Table 1. Continued

Variable	DAPT ≤1 y, n=900	DAPT >1 y, n=2301	*P* value
Total stent length, mm	34 (23–54)	38 (24–58)	0.016
DAPT score	2 (1–2)	2 (1–2)	0.667
DAPT score≥2, n (%)	500 (55.6)	1260 (54.8)	0.684
Medications at discharge			
Aspirin, n (%)	900 (100)	2301 (100)	NA
$P2Y_{12}$ receptor inhibitor, n (%)	900 (100)	2301 (100)	NA
Oral anticoagulant, n (%)	2 (0.3)	4 (0.3)	1.000
β-Blockers, n (%)	823 (91.4)	2116 (92.0)	0.632
Statins, n (%)	862 (95.8)	2220 (96.5)	0.345
Calcium channel blockers, n (%)	405 (45.0)	1088 (47.3)	0.244
Antiplatelet drugs at 6 mo	n=900	n=2301	
Aspirin, n (%)	891 (99.0)	2301 (100)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	888 (98.7)	2301 (100)	<0.001
Antiplatelet drugs at 12 mo	n=900	n=2301	
Aspirin, n (%)	868 (96.4)	2301 (100)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	827 (91.9)	2301 (100)	<0.001
Antiplatelet drugs at 18 mo	n=899	n=2297	
Aspirin, n (%)	833 (92.7)	2293 (99.8)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	24 (2.7)	2120 (92.3)	<0.001
Antiplatelet drugs at 24 mo	n=899	n=2287	
Aspirin, n (%)	830 (92.3)	2248 (98.3)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	22 (2.4)	966 (42.2)	<0.001
Antiplatelet drugs at 30 mo	n=259	n=1009	
Aspirin, n (%)	228 (88.0)	985 (97.6)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	12 (4.6)	306 (30.3)	<0.001
Mean DAPT time, d	350±56	667±166	<0.001
Median DAPT time, d	365 (365–365)	548 (548–810)	<0.001

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; EES, everolimus-eluting stent; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; NA, not appliable. PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery; WBC, white blood cell; and ZES, zotarolimus-eluting stent.

after IPTW analysis (Figure S1 and Figure S2), and it obtained consistent results that the risks of MACCE, all-cause death, and definite/probable ST were significantly decreased in the prolonged DAPT group. However, the risk of clinically relevant bleeding in the prolonged DAPT group was almost twice that of the shortened DAPT group, although no statistical difference was found (1.3% versus 0.7%; adjusted HR, 1.733 [95% CI, 0.716–4.196]; IPTW HR, 1.851 [95% CI, 0.766–4.473]).

Lp(a) Levels and 2.5-Year Clinical Outcomes

Clinical outcomes according to Lp(a) levels are shown in Table S2 and Figure S3. The risks of MACCE (2.6% versus 1.4%; adjusted HR, 1.733 [95% CI, 1.023–2.934]) and definite/probable ST (0.7% versus 0.2%; adjusted HR, 3.297 [95% CI, 1.060–10.251]) were higher in patients with elevated Lp(a) levels than those with normal Lp(a) levels. After IPTW adjustment, all the candidate variables were well balanced between the 2 groups with absolute standardized differences <10% (Figure S4 and Figure S5), and it showed that patients with elevated Lp(a) levels were significantly associated with increased risk of MACCE (HR, 1.695 [95% CI, 1.005–2.860]) and definite/probable ST (HR, 3.157 [95% CI, 1.015–9.822]) than those with normal Lp(a) concentrations.

DAPT ≤1 Year Versus DAPT >1 Year in Patients With Elevated and Normal Lp(a) Levels

Among patients with elevated Lp(a) levels, DAPT >1 year presented lower risk of MACCE (1.9% versus 4.5%; adjusted HR, 0.344 [95% CI, 0.159–0.744]) compared with DAPT ≤1 year. The risks of all-cause death (0% versus 3.1%), cardiac death (0% versus 2.1%),

Table 2. Baseline Patient, Angiographic, and Procedural Characteristics According to Lp(a) Levels and DAPT Duration

Variable	Lp(a) ≤30 mg/dL, n=2124			Lp(a) >30 mg/dL, n=1077		
	DAPT ≤1 y, n=608	DAPT >1 y, n=1516	*P* value	DAPT≤1 y, n=292	DAPT >1 y, n=785	*P* value
Age, y	58 (50–64)	58 (50–64)	0.839	59 (50–65)	59 (52–65)	0.303
Men, n (%)	492 (80.9)	1243 (82.0)	0.564	231 (79.1)	617 (78.6)	0.855
Body mass index, kg/m^2	26.0 (24.2–28.3)	26.0 (24.2–27.8)	0.474	25.9 (24.0–27.7)	25.8 (23.9–27.7)	0.558
Current smoker, n (%)	359 (59.0)	869 (57.3)	0.467	161 (55.1)	419 (53.4)	0.606
Diabetes, n (%)	195 (32.1)	472 (31.1)	0.674	87 (29.8)	229 (29.2)	0.842
Hypertension, n (%)	384 (63.2)	983 (64.8)	0.464	183 (62.7)	510 (65.0)	0.484
Dyslipidemia, n (%)	414 (68.1)	1060 (69.9)	0.408	199 (68.2)	545 (69.4)	0.687
Previous myocardial infarction, n (%)	155 (25.5)	434 (28.6)	0.145	83 (28.4)	240 (30.6)	0.494
Previous PCI, n (%)	172 (28.3)	433 (28.6)	0.900	92 (31.5)	223 (28.4)	0.320
Previous CABG, n (%)	18 (3.0)	62 (4.1)	0.217	11 (3.8)	46 (5.9)	0.173
Previous stroke, n (%)	64 (10.5)	138 (9.1)	0.312	34 (11.6)	90 (11.5)	0.935
Peripheral vascular disease, n (%)	16 (2.6)	53 (3.5)	0.310	7 (2.4)	30 (3.8)	0.254
Chronic kidney disease, n (%)	52 (8.6)	144 (9.5)	0.496	22 (7.5)	83 (10.6)	0.135
COPD, n (%)	9 (1.5)	30 (2.0)	0.439	5 (1.7)	23 (2.9)	0.264
LVEF, %	65 (60–68)	64 (60–68)	0.338	65 (60–69)	64 (60–68)	0.131
LVEF <50%, n (%)	19 (3.2)	56 (3.8)	0.502	9 (3.2)	40 (5.2)	0.172
Systolic blood pressure, mm Hg	122 (120–140)	126 (120–140)	0.220	130 (120–140)	125 (120–140)	0.172
Laboratory data						
WBC, 10^3/μL	6.45 (5.34–7.52)	6.40 (5.41–7.44)	0.534	6.58 (5.55–7.41)	6.25 (5.38–7.45)	0.082
Hemoglobin, g/L	146 (136–155)	146 (136–155)	0.873	145 (135–153)	144 (134–154)	0.885
Total cholesterol, mmol/L	3.88 (3.42–4.68)	3.93 (3.30–4.72)	0.691	4.12 (3.54–4.96)	4.12 (3.45–4.86)	0.340
LDL-C, mmol/L	2.23 (1.84–2.91)	2.26 (1.75–2.90)	0.459	2.44 (1.97–3.16)	2.39 (1.90–3.08)	0.270
HDL-C, mmol/L	1.01 (0.86–1.16)	1.00 (0.85–1.17)	0.286	1.04 (0.91–1.20)	1.04 (0.89–1.21)	0.832
HbA1c, %	6.2 (5.9–6.9)	6.2 (5.9–6.9)	0.330	6.2 (5.8–7.0)	6.2 (5.9–6.9)	0.569
Lp(a), mg/dL	9.9 (4.7–17.4)	9.7 (5.1–16.6)	0.789	51.5 (39.2–73.8)	52.4 (39.3–73.9)	0.777
Radial artery access, n (%)	519 (91.9)	1292 (92.3)	0.750	239 (91.6)	643 (89.3)	0.298
SYNTAX score	9 (6–16)	10 (7–17)	0.024	11 (7–17)	10 (6–18)	0.669
SYNTAX score >22, n (%)	60 (10.1)	167 (11.3)	0.427	33 (11.8)	93 (12.5)	0.771
Total lesion length, mm	31 (18–49)	33 (20–55)	0.035	33 (20–56)	34 (21–55)	0.497
Target lesion morphology						
Bifurcation lesion, n (%)	106 (17.4)	355 (23.4)	0.003	61 (20.9)	173 (22.0)	0.685
Two-stent technique, n (%)	14 (2.3)	84 (5.5)	0.001	12 (4.1)	42 (5.4)	0.407
Chronic total occlusion, n (%)	108 (17.8)	267 (17.6)	0.934	56 (19.2)	161 (20.5)	0.628
In-stent restenosis, n (%)	29 (4.8)	72 (4.7)	0.984	14 (4.8)	38 (4.8)	0.975
Severe calcification, n (%)	21 (3.5)	59 (3.9)	0.632	13 (4.5)	23 (2.9)	0.217
Angulation >45 degrees, n (%)	60 (9.9)	176 (11.6)	0.248	34 (11.6)	100 (12.7)	0.628
Type B2 or C lesion, n (%)	456 (75.0)	1180 (77.8)	0.160	229 (78.4)	638 (81.3)	0.294
No. vessels treated	1 (1–1)	1 (1–1)	0.825	1 (1–2)	1 (1–2)	0.431
No. lesions treated	1 (1–2)	1 (1–2)	0.481	1 (1–2)	1 (1–2)	0.898
No. lesions treated ≥3, n (%)	41 (6.7)	113 (7.5)	0.568	23 (7.9)	55 (7.0)	0.624
Drug-eluting stent number	2 (1–2)	2 (1–3)	0.001	2 (1–3)	2 (1–3)	0.595
Drug-eluting stent number ≥ 3, n (%)	123 (20.2)	407 (26.8)	0.001	80 (27.4)	207 (26.4)	0.734
Type of drug-eluting stent			0.311			0.031
PES/SES, n (%)	281 (46.2)	664 (43.8)		145 (49.7)	332 (42.3)	
EES/ZES, n (%)	327 (53.8)	852 (56.2)		147 (50.3)	453 (57.7)	

(*Continued*)

Table 2. Continued

Variable	Lp(a) ≤30 mg/dL, n=2124			Lp(a) >30 mg/dL, n=1077		
	DAPT ≤1 y, n=608	DAPT >1 y, n=1516	*P* value	DAPT≤1 y, n=292	DAPT >1 y, n=785	*P* value
Minimum stent diameter, mm	2.75 (2.50–3.00)	2.75 (2.50–3.00)	0.958	2.75 (2.50–3.00)	2.75 (2.50–3.00)	0.544
Total stent length, mm	33 (23–53)	37 (23–58)	0.013	36 (23–59)	38 (24–60)	0.547
DAPT score	2 (1–2)	2 (1–2)	0.730	2 (1–3)	2 (1–2)	0.406
DAPT score≥2, n (%)	333 (54.8)	842 (55.5)	0.747	167 (57.2)	418 (53.2)	0.248
Medications at discharge						
Aspirin, n (%)	600 (98.7)	1500 (98.9)	0.608	289 (99.0)	776 (98.9)	1.000
$P2Y_{12}$ receptor inhibitor, n (%)	599 (98.5)	1498 (98.8)	0.586	287 (98.3)	776 (98.9)	0.466
Oral anticoagulant, n (%)	1 (0.2)	3 (0.3)	1.000	1 (0.5)	1 (0.2)	0.485
β-Blockers, n (%)	558 (91.8)	1386 (91.4)	0.793	265 (90.8)	730 (93.0)	0.218
Statins, n (%)	581 (95.6)	1459 (96.2)	0.467	281 (96.2)	761 (96.9)	0.559
Calcium channel blockers, n (%)	271 (44.6)	713 (47.0)	0.304	134 (45.9)	375 (47.8)	0.583
Antiplatelet drugs at 6 mo	n=608	n=1516		n=292	n=785	
Aspirin, n (%)	601 (98.8)	1516 (100)	<0.001	290 (99.3)	785 (100)	0.073
$P2Y_{12}$ receptor inhibitor, n (%)	600 (98.7)	1516 (100)	<0.001	278 (95.2)	785 (100)	<0.001
Antiplatelet drugs at 12 mo	n=608	n=1516		n=292	n=785	
Aspirin, n (%)	590 (97.0)	1516 (100)	<0.001	278 (95.2)	785 (100)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	561 (92.3)	1516 (100)	<0.001	266 (91.1)	785 (100)	<0.001
Antiplatelet drugs at 18 mo	n=607	n=1512		n=292	n=785	
Aspirin, n (%)	563 (92.8)	1509 (99.8)	<0.001	270 (92.5)	784 (99.9)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	16 (2.6)	1393 (92.1)	<0.001	8 (2.7)	727 (92.6)	<0.001
Antiplatelet drugs at 24 mo	n=607	n=1504		n=292	n=783	
Aspirin, n (%)	560 (92.3)	1475 (98.1)	<0.001	270 (92.5)	773 (98.7)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	16 (2.6)	626 (41.6)	<0.001	6 (2.1)	340 (43.4)	<0.001
Antiplatelet drugs at 30 mo	n=165	n=668		n=94	n=341	
Aspirin, n (%)	145 (87.9)	649 (97.2)	0.003	83 (88.3)	336 (97.6)	<0.001
$P2Y_{12}$ receptor inhibitor, n (%)	8 (4.8)	180 (26.9)	<0.001	4 (4.3)	126 (37.0)	<0.001
Mean DAPT time, d	349±59	662±163	<0.001	353±50	677±172	<0.001
Median DAPT time, d	365 (365–365)	548 (548–803)	<0.001	365 (365–365)	548 (54–834)	<0.001

CABG indicates 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; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; PES, paclitaxel-eluting stent; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; WBC, white blood cell; and ZES, zotarolimus-eluting stent.

and definite/probable ST (0.3% versus 2.1%; adjusted HR, 0.099 [95% CI, 0.019–0.512]) were also significantly lower in the DAPT >1 year group than that in the DAPT ≤1 year group. Moreover, the risk of clinically relevant bleeding was not statistical different between the prolonged and shortened DAPT groups (1.5% versus 1.0%; adjusted HR, 1.172 [95% CI, 0.318–4.321]) (Table S3, Figure 3A and Figure 4A). In contrast, no statistically significant difference was found between the DAPT >1 year and DAPT ≤1 year groups with respect to MACCE (1.3% versus 1.6%; adjusted HR, 0.775 [95% CI, 0.356–1.687]) and definite/probable ST (0.1% versus 0.5%; adjusted HR, 0.142 [95% CI, 0.017–1.165]) in patients with normal Lp(a) levels. Patients who received DAPT >1 year had lower risks of all-cause mortality (0.1% versus 1.2%; adjusted HR, 0.092 [95% CI, 0.017–0.485]) and cardiac mortality (0% versus 0.7%) compared with those with DAPT ≤1 year. Notably, prolonged DAPT had 2.4-times higher risk of Bleeding Academic Research Consortium type 2, 3, or 5 bleeding than shortened DAPT, though without statistical difference (1.2% versus 0.5%; adjusted HR, 2.249 [95% CI, 0.658–7.689]) (Table S3, Figure 3B and Figure 4B).

After IPTW adjustment, all the candidate variables were well balanced between the DAPT ≤1 year and DAPT >1 year groups for both patients with normal and elevated Lp(a) levels (Figure 5, Figure S6 and Figure S7). Similar to the results of multivariable-adjusted analysis, the IPTW analysis demonstrated that patients

Table 3. Two-Year Clinical Outcomes According to DAPT Duration

Clinical end point	No. patients with event, n (%)		Crude HR (95% CI)	Multivariable adjusted HR (95% CI)	IPTW adjusted HR (95% CI)
	DAPT ≤1 y	DAPT >1 y			
All-cause death/MI/stroke	23 (2.6)	35 (1.5)	0.566 (0.334–0.958)	0.536 (0.313–0.915)	0.514 (0.303–0.874)
All-cause death	16 (1.8)	2 (0.1)	0.049 (0.011–0.212)	0.045 (0.010–0.198)	0.040 (0.009–0.175)
Cardiac death	10 (1.1)	0 (0)	NA	NA	NA
Nonfatal MI	5 (0.6)	13 (0.6)	0.981 (0.349–2.754)	1.043 (0.367–2.964)	0.827 (0.282–2.426)
Stroke	7 (0.8)	22 (1.0)	1.152 (0.491–2.701)	1.077 (0.452–2.567)	1.033 (0.440–2.423)
Definite/probable ST	9 (1.0)	4 (0.2)	0.168 (0.052–0.546)	0.150 (0.046–0.498)	0.142 (0.043–0.470)
BARC type 2, 3, or 5 bleeding	6 (0.7)	30 (1.3)	1.829 (0.760–4.399)	1.733 (0.716–4.196)	1.851 (0.766–4.473)

Variables included in Cox multivariable model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous stroke, peripheral vascular disease, low-density lipoprotein cholesterol, SYNTAX score, total lesion length, bifurcation lesion, minimum stent diameter, total stent length, and use of statin at discharge. Variables included in IPTW model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous percutaneous coronary intervention, previous stroke, peripheral vascular disease, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein cholesterol, total lesion length, type B2 or C lesion, chronic total occlusion, bifurcation lesion, number of lesions treated, stent number, use of everolimus- or zotarolimus-eluting stent, and use of β-blocker and statin at discharge. BARC indicates Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NA, not appliable; ST, stent thrombosis; and SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.

who received DAPT >1 year had lower risks of MACCE (HR, 0.351 [95% CI, 0.164–0.751]) and definite/probable ST (HR, 0.092 [95% CI, 0.018–0.469]) than those who received DAPT ≤1 year in patients with elevated Lp(a) levels (Figure 4A), whereas prolonged DAPT was not associated with reduced risk of MACCE and definite/probable ST in patients with normal Lp(a) levels (Figure 4B).

DISCUSSION

To our knowledge, this is the first study to evaluate the effect of Lp(a) concentrations on the efficacy and safety of prolonged DAPT for stable patients with CAD who underwent PCI. The principal findings are: (1) Elevated Lp(a) levels were significantly associated with increased MACCE (death, MI, or stroke) and definite or probable ST in stable patients with CAD after PCI with a DES in the era of statin therapy. (2) Among patients with elevated Lp(a) levels, prolonged DAPT was associated with lower risks of MACCE and definite or probable ST without statistically increasing the clinically relevant bleeding, whereas in patients with normal Lp(a) levels, prolonged DAPT did not show statistically significant evidence of benefit for reducing MACCE and definite/probable ST, and it tended to increase the risk of clinically relevant bleeding after 2.5 years.

Lp(a) has been recognized as a risk factor for cardiovascular disease in recent years. In 2008, Kamstrup et al reported that extreme Lp(a) levels (≥120 mg/dL) predict a 3- to 4-fold increase in risk of MI in 9330 general participants from the Copenhagen City Heart Study.[3] Since then, a growing body of evidence from meta-analyses,[2,5] Mendelian randomization studies,[6,8] and genome-wide association studies[4,7] has demonstrated that Lp(a) is an independent, genetic, and causal risk factor for CAD. Recently, Liu et al reported that high Lp(a) levels are associated with higher incidence of a composite of cardiac death, MI, or stroke in stable patients with CAD treated with statins after PCI at a 4.9-year follow-up.[12] A study with 1768 patients who received statin therapy after PCI also found that elevated Lp(a) levels were associated with increased cardiac death or ACS during a median follow-up of 4.4 years (adjusted HR, 1.28 [95% CI, 1.04–1.58]).[10] Similarly, we found a positive association between Lp(a) levels and subsequent composite ischemic events as well as definite or probable ST during a median follow-up of 2.5 years. This finding was confirmed by Cox regression analysis and IPTW analysis.

However, there are currently no approved pharmacologic therapies that specifically target high Lp(a) levels. The commonly used statins have no Lp(a) lowering effect, and a close assessment of published studies has even indicated a slight Lp(a) increasing effect. Though having a 20% to 30% Lp(a)-lowering effects, both niacin and mipomersen are associated with side effects, and mipomersen is only approved in homozygous familial hypercholesterolemia caused by hepatotoxicity. A post hoc analysis of the evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab trial indicated that Lp(a) lowering by proprotein convertase subtilisin/kexin type 9 inhibitor contributed independently to cardiovascular event reduction in patients with ACS, yet each 5-mg/dL reduction in Lp(a) only predicted a 2.5% relative reduction in cardiovascular events.[26] However, several Mendelian randomization analyses speculated

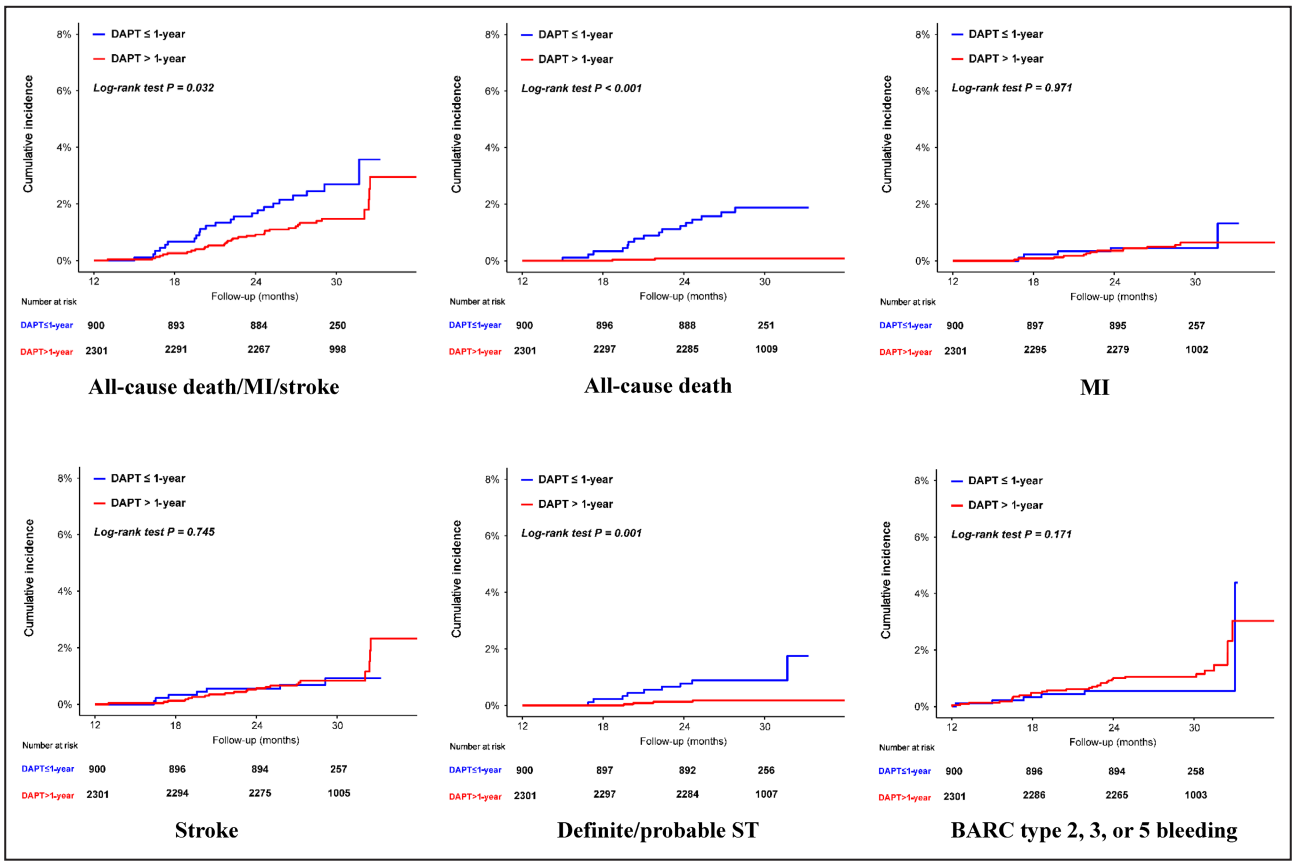

Figure 2. Kaplan–Meier curves for 2.5-year clinical outcomes according to DAPT duration (>1 year vs ≤1 year) in overall population.
BARC indicates Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; MI, myocardial infarction; and ST, stent thrombosis.

that ≈66 to 100 mg/dL reduction of Lp(a) may be required to achieve equivalent protective effects yielded from a 39-mg/dL (or 1 mmol/L) reduction of low-density lipoprotein cholesterol.[27,28] Although Tsimikas et al found that a novel therapeutic agent, apoA-L_{Rx}, provides potent reductions in levels of Lp(a) in patients with cardiovascular disease by reducing the production of apoA, which offers greater specificity than proprotein convertase subtilisin/kexin type 9 inhibitor. Further trials are needed to assess the impact of Lp(a) lowering with apoA-L_{Rx} on ischemic events in patients with established CAD.[14]

Lp(a) is composed of a low-density lipoprotein cholesterol–like particle and an apoA, the pathognomonic component of Lp(a) that binds to apolipoprotein B100 via a disulfide bond. Because of the similarity between apoA and plasminogen, Lp(a) promotes thrombotic and fibrinolytic events through several mechanisms, including inflammation through its content of oxidized phospholipids, the presence of lysine binding sites that allow accumulation in the arterial wall, and potential antifibrinolytic roles by inhibiting plasminogen activation.[15,16] DAPT, consisting of aspirin and a $P2Y_{12}$ inhibitor, represents the cornerstone of treatment to preventing thrombotic complications in patients with CAD undergoing PCI. Current guidelines on DAPT from Europe and the United States recommend aspirin indefinitely and clopidogrel for 6 months after implantation of a DES in stable patients with CAD, and DAPT prolongation beyond 6 months and up to 30 months may be considered in stable patients with CAD who are at low bleeding risk but high thrombotic risk.[29] In real-world clinical practice, almost all stable patients with CAD received DAPT for 6 to 12 months or >12 months after PCI with a DES in our center in 2013. In this setting, we compared the relative efficacy and safety of prolonged DAPT (>1 year) versus shortened DAPT (≤1 year) in patients with elevated Lp(a) levels and normal Lp(a) levels, respectively, and we hypothesized that patients with stable CAD and elevated Lp(a) levels would derive benefit from continuing DAPT beyond 12 months.

Potentially, the important finding of our study is that prolonged DAPT could reduce the risks of 2.5-year MACCE and definite or probable ST, without statistically increasing clinically relevant bleeding for stable patients with CAD with elevated Lp(a) levels after PCI with a DES. In contrast, prolonged DAPT was not significantly

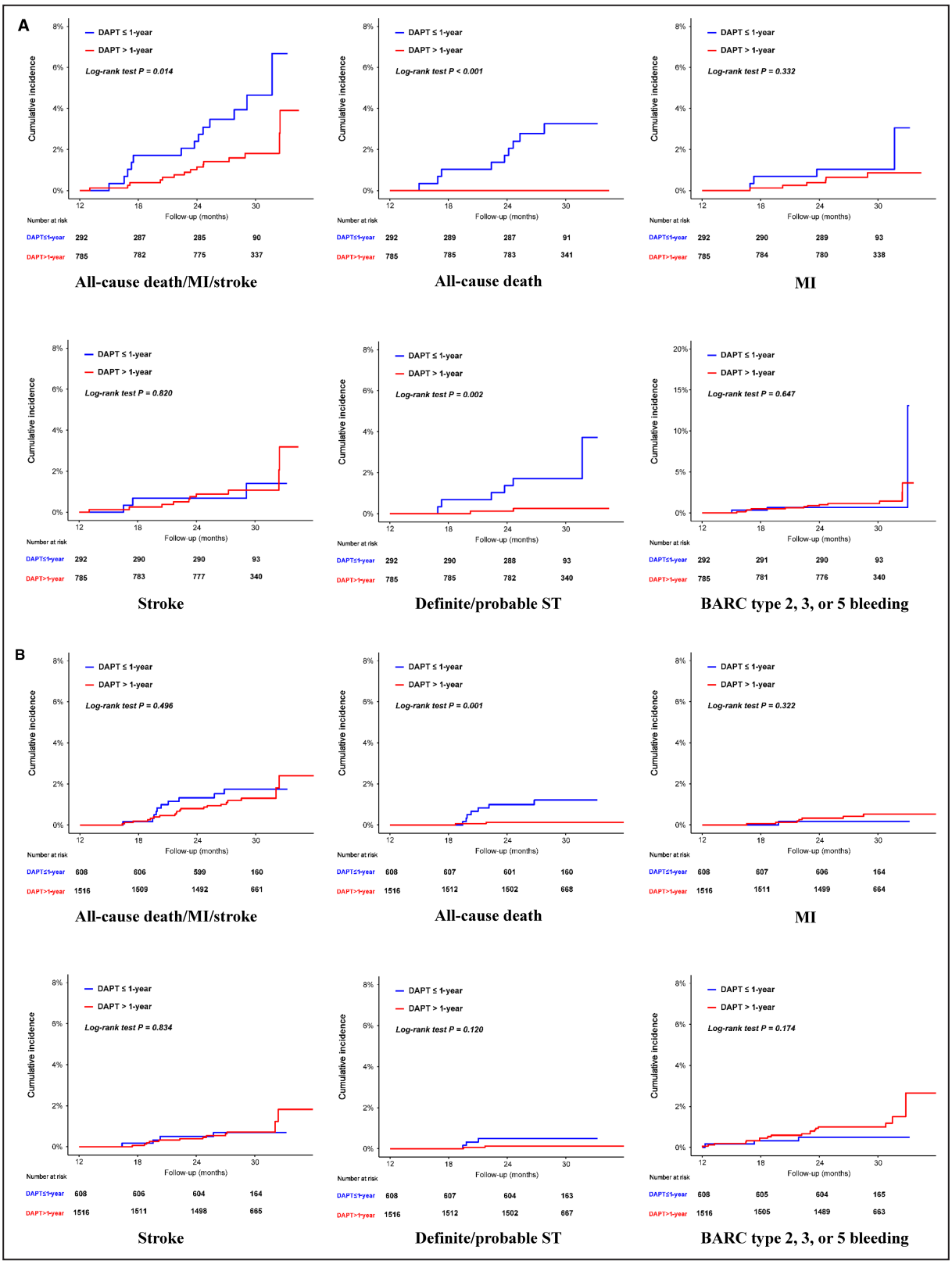

Figure 3. Kaplan-Meier curves for 2.5-year clinical outcomes according to DAPT duration (>1 year vs ≤1 year) in patients with (A) Lp(a) levels >30 mg/dL and (B) Lp(a) levels ≤30 mg/dL, respectively.
BARC indicates Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; Lp(a), lipoprotein(a); MI, myocardial infarction; and ST, stent thrombosis.

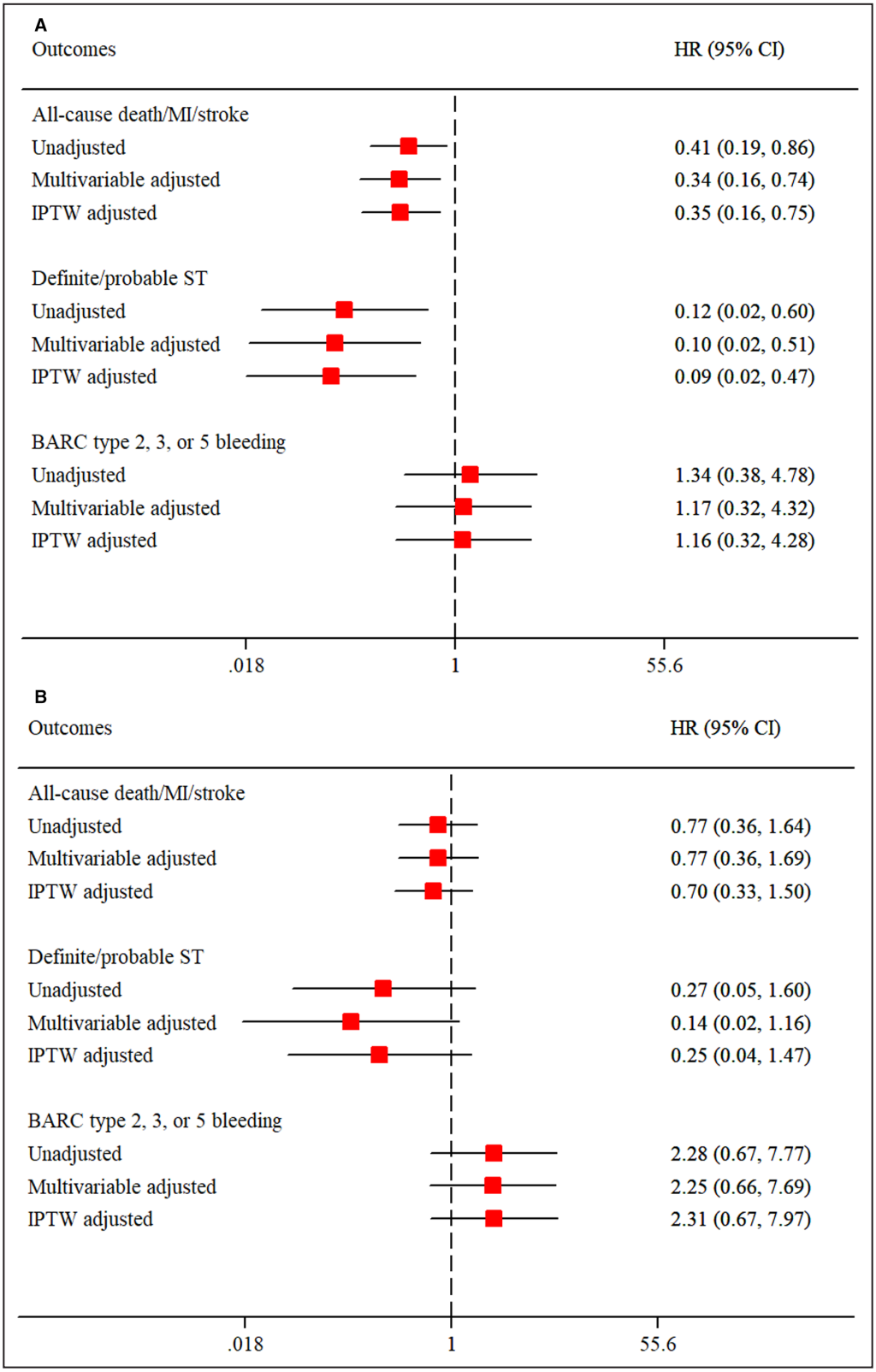

Figure 4. Unadjusted and adjusted association between DAPT duration and main clinical outcomes in patients with (A) Lp(a) levels >30 mg/dL and (B) Lp(a) levels ≤30 mg/dL, respectively. BARC indicates Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; HR, hazard ratio; Lp(a), lipoprotein(a); MI, myocardial infarction; and ST, stent thrombosis.

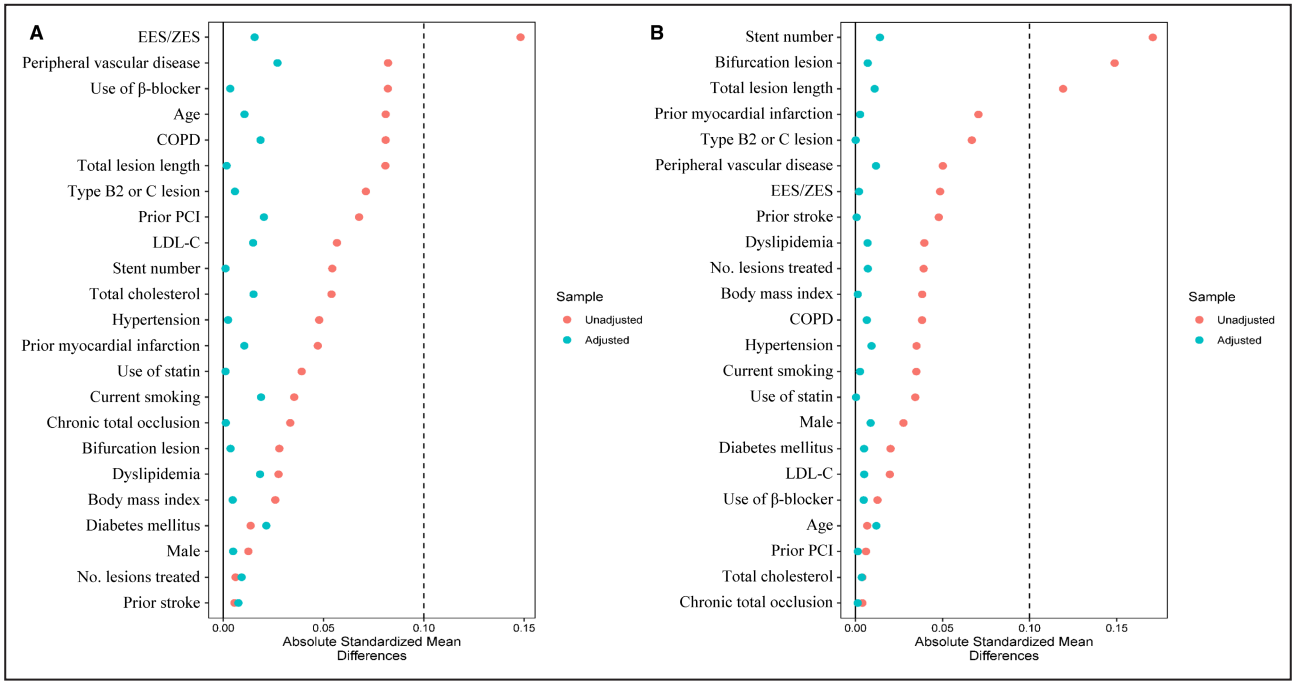

Figure 5. Absolute standard difference before and after inverse probability of treatment weighting analysis between the DAPT >1 year and DAPT ≤1 year groups in patients with (A) Lp(a) levels >30 mg/dL and (B) Lp(a) levels ≤30 mg/dL, respectively. COPD indicates chronic obstructive pulmonary disease; EES, everolimus-eluting stent; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCI, percutaneous coronary intervention; and ZES, zotarolimus-eluting stent.

associated with reduced incidence of the composite ischemic events in patients with normal Lp(a) levels. Furthermore, though without statistical difference, prolonged DAPT tended to increase the clinically relevant bleeding risk in this cohort of patients. The multicenter, randomized Ticagrelor in Patients with Diabetes and Stable Coronary Artery Disease with a History of Previous Percutaneous Coronary Intervention trial reported that the addition of ticagrelor to aspirin significantly reduced 3.3-year cardiovascular death, MI, or stroke, and provided a favorable net clinical benefit in patients with diabetes and stable CAD who had a history of PCI.[30] Stable patients with CAD with elevated Lp(a) levels were at heightened risk for ischemic events, and our study demonstrated that these patients can also benefit from prolonging DAPT duration after PCI with a DES. In this setting, Lp(a) levels might be an important consideration when deciding upon the duration of DAPT for stable patients with CAD in the future.

Our study presented several limitations. First, this is a single-center, nonrandomized study; thus, it is limited by unbalanced baseline characteristics and selection bias. Actually, the duration of DAPT was not predefined but was individualized by physician discretion and patient preference. Although multivariable-adjusted analysis and IPTW analysis were performed, it was hard to control all the confounding factors and eliminate the selection bias. Second, our findings were mainly derived from subgroup analysis of the cohort study; thus, we might have inadequate statistical power to provide a definitive answer on the relative efficacy and safety of prolonged DAPT in patients with elevated Lp(a) and normal Lp(a) levels, respectively. In this setting, the results should be interpreted as hypothesis generating. Third, the DAPT regimen in our study was based on the use of clopidogrel and aspirin; the clinical impact of DAPT >1 year with using a potent $P2Y_{12}$ inhibitor plus aspirin according to Lp(a) concentrations in this population is unclear. Moreover, the results cannot be extrapolated to other patient populations, such as the ACS population. Fourth, Lp(a) was measured as mass concentration but not particle concentration; thus, variations of apoA size between assay calibrators and patients' samples might overestimate or underestimate the real level of Lp(a).

CONCLUSIONS

In stable patients with CAD who underwent PCI, elevated Lp(a) levels were positively related to ischemic events at a 2.5-year follow-up. Prolonged DAPT (>1 year) was associated with reduced risk of cardiovascular events among patients with elevated Lp(a) levels, whereas it did not show statistically significant evidence of benefit for reducing ischemic events and tended to increase clinically relevant bleeding in patients with

normal Lp(a) levels. Further well-designed randomized trials are needed to confirm these findings.

Acknowledgments

Author contributions: Concept and design: Drs Cui, Feng, and Dou. Acquisition, analysis, or interpretation of data: Drs Cui, Yin, Feng, Zhu, Song, Wang, Jia, Zhang, Wang, and Cai. Drafting of the article: Dr Cui. Critical revision of the article for important intellectual content: all authors. Statistical analysis: Drs Cui, Zhang, Wang, and Cai. Administrative, technical, or material support: Drs Feng and Dou. Supervision: Drs Cui, Feng, and Dou.

Sources of Funding

The current study was funded by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2021-I2 M-1-008) and Beijing Municipal Health Commission-Capital Health Development Research Project (2020-1-4032).

ARTICLE INFORMATION

Received August 10, 2021; accepted March 14, 2022.

Affiliation

Cardiometabolic Medicine Center, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S7

REFERENCES

1. Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, Orringer CE. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13:374–392. doi: 10.1016/j.jacl.2019.04.010
2. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation*. 2000;102:1082–1085. doi: 10.1161/01.CIR.102.10.1082
3. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. 2008;117:176–184. doi: 10.1161/CIRCULATIONAHA.107.715698
4. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361:2518–2528. doi: 10.1056/NEJMoa0902604
5. Collaboration ERF, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–423.
6. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301:2331–2339. doi: 10.1001/jama.2009.801
7. Wei WQ, Li X, Feng Q, Kubo M, Kullo IJ, Peissig PL, Karlson EW, Jarvik GP, Lee MTM, Shang N, et al. LPA variants are associated with residual cardiovascular risk in patients receiving statins. *Circulation*. 2018;138:1839–1849.
8. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. *Eur Heart J*. 2019;40:2760–2770. doi: 10.1093/eurheartj/ehy902
9. O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, Desai NR, Solomon SD, Domanski M, Arai K, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *J Am Coll Cardiol*. 2014;63:520–527. doi: 10.1016/j.jacc.2013.09.042
10. Suwa S, Ogita M, Miyauchi K, Sonoda T, Konishi H, Tsuboi S, Wada H, Naito R, Dohi T, Kasai T, et al. Impact of lipoprotein (a) on long-term outcomes in patients with coronary artery disease treated with statin after a first percutaneous coronary intervention. *J Atheroscler Thromb*. 2017;24:1125–1131. doi: 10.5551/jat.38794
11. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018;392:1311–1320. doi: 10.1016/S0140-6736(18)31652-0
12. Liu H-H, Cao Y-X, Jin J-L, Zhang H-W, Hua QI, Li Y-F, Guo Y-L, Zhu C-G, Wu N-Q, Xu R-X, et al. Predicting cardiovascular outcomes by baseline lipoprotein(a) concentrations: a large cohort and long-term follow-up study on real-world patients receiving percutaneous coronary intervention. *J Am Heart Assoc*. 2020;9:e014581. doi: 10.1161/JAHA.119.014581
13. Shah NP, Wang Q, Wolski KE, Cho L, McErlean E, Ruotolo G, Weerakkody G, Riesmeyer JS, Nicholls SJ, Lincoff AM, et al. The role of lipoprotein (a) as a marker of residual risk in patients with diabetes and established cardiovascular disease on optimal medical therapy: post hoc analysis of ACCELERATE. *Diabetes Care*. 2020;43:e22–e24. doi: 10.2337/dc19-1117
14. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif J-C, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med*. 2020;382:244–255. doi: 10.1056/NEJMoa1905239
15. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69:692–711. doi: 10.1016/j.jacc.2016.11.042
16. Tsimikas S, Fazio S, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, Moriarty PM, Rader DJ, Remaley AT, Reyes-Soffer G, et al. NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J Am Coll Cardiol*. 2018;71:177–192.
17. Zhang D, Yan R, Gao G, Wang H, Fu R, Li J, Yin D, Zhu C, Feng L, Song W, et al. Validating the performance of 5 risk scores for major adverse cardiac events in patients who achieved complete revascularization after percutaneous coronary intervention. *Can J Cardiol*. 2019;35:1058–1068. doi: 10.1016/j.cjca.2019.02.017
18. Wang HY, Cai ZX, Yin D, Song WH, Feng L, Gao RL, Yang YJ, Dou KF. Optimal strategy for antiplatelet therapy after coronary drug-eluting stent implantation in high-risk "TWILIGHT-like" patients with diabetes mellitus. *Front Cardiovasc Med*. 2020;7:586491. doi: 10.3389/fcvm.2020.586491
19. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407. doi: 10.1056/NEJMoa1915922
20. Wang HY, Dou KF, Wang Y, Yin D, Xu B, Gao RL. Benefit-risk profile of DAPT continuation beyond 1 year after PCI in patients with high thrombotic risk features as endorsed by 2018 ESC/EACTS myocardial revascularization guideline. *Cardiovasc Drugs Ther*. 2020;34:663–675.
21. Zhu JR, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ, Chen H, Chen WW, Chen WX, Dong YG, et al. 2016 Chinese guideline for the management of dyslipidemia in adults. *Chin J Cardiol*. 2016;44:833–853.
22. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J Jr, Grover S, Gupta M, et al. 2016 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2016;32:1263–1282.
23. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551–2567.
24. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Gabriel Steg P, Morel M-A, Mauri L, Vranckx P, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313
25. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
26. Szarek M, Bittner VA, Aylward P, Baccara-Dinet M, Bhatt DL, Diaz R, Fras Z, Goodman SG, Halvorsen S, Harrington RA, et al. Lipoprotein(a) lowering by

alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. *Eur Heart J*. 2020;41:4245–4255. doi: 10.1093/eurheartj/ehaa649

27. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, Willeit P, Young R, Surendran P, Karthikeyan S, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol*. 2018;3:619–627.
28. Lamina C, Kronenberg F, Lp(a)-GWAS-Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol*. 2019;4:575–579. doi: 10.1001/jamacardio.2019.1041
29. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. *J Am Coll Cardiol*. 2018;72:2915–2931.
30. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet*. 2019;394:1169–1180.

SUPPLEMENTAL MATERIAL

Table S1. Baseline patient, angiographic and procedural characteristics according to Lp(a) levels.

Variable	Lp(a) ≤ 30mg/dL (n=2124)	Lp(a) > 30mg/dL (n=1077)	P value
Age, years	58 (50-64)	59 (51-65)	**0.009**
Male, n (%)	1735 (81.7)	848 (78.7)	**0.046**
Body mass index, kg/m^2	26.0 (24.2-28.0)	25.8 (23.9-27.7)	**0.048**
Current smoker, n (%)	1228 (57.8)	580 (53.9)	**0.033**
Diabetes mellitus, n (%)	667 (31.4)	316 (29.3)	0.232
Hypertension, n (%)	1367 (64.4)	693 (64.3)	0.994
Dyslipidemia, n (%)	1474 (69.4)	744 (69.1)	0.854
Previous myocardial infarction, n (%)	589 (27.7)	323 (30.0)	0.181
Previous PCI, n (%)	605 (28.5)	315 (29.2)	0.652
Previous CABG, n (%)	80 (3.8)	57 (5.3)	**0.044**
Previous stroke, n (%)	202 (9.5)	124 (11.5)	0.077
Peripheral vascular disease, n (%)	69 (3.2)	37 (3.4)	0.780
Chronic kidney disease, n (%)	105 (9.7)	196 (9.2)	0.633
COPD, n (%)	39 (1.8)	28 (2.6)	0.154
LVEF, %	64 (60-68)	64 (60-68)	0.603
LVEF<50%, n (%)	75 (3.6)	49 (4.7)	0.155
Systolic blood pressure, mmHg	125 (120-140)	128 (120-140)	0.843
Laboratory data			
WBC, 10^3/uL	6.41 (5.39-7.46)	6.35 (5.43-7.45)	0.981
Hemoglobin, g/L	146 (136-155)	145 (134-154)	**0.014**
Total cholesterol, mmol/L	3.92 (3.34-4.71)	4.12 (3.47-4.90)	< **0.001**
LDL-C, mmol/L	2.24 (1.78-2.90)	2.40 (1.94-3.10)	< **0.001**
HDL-C, mmol/L	1.00 (0.85-1.17)	1.04 (0.89-1.21)	< **0.001**
HbA1c, %	6.2 (5.9-6.9)	6.2 (5.9-6.9)	0.977
Lp(a), mg/dL	9.8 (5.0-16.8)	52.1 (39.3-73.9)	< **0.001**
Radial artery access, n (%)	1811 (92.2)	882 (89.9)	**0.040**
Multivessel disease, n (%)	1604 (75.5)	841 (78.1)	0.106

SYNTAX score	10 (6-16)	10 (7-18)	0.052
SYNTAX score >22, n (%)	227 (11.0)	126 (12.3)	0.279
Total lesion length, mm	32 (20-54)	34 (21-55)	**0.034**
Target lesion morphology			
Bifurcation lesion, n (%)	461 (21.7)	234 (21.7)	0.988
2-stent technique, n (%)	98 (4.6)	54 (5.0)	0.615
Chronic total occlusion, n (%)	375 (17.7)	217 (20.1)	0.086
In-stent restenosis, n (%)	101 (4.8)	52 (4.8)	0.927
Severe calcification, n (%)	80 (3.8)	36 (3.3)	0.544
Angulation > 45 degrees	236 (11.1)	134 (12.4)	0.266
Type B2 or C lesion, n (%)	1636 (77.0)	867 (80.5)	**0.024**
No. vessels treated	1 (1-1)	1 (1-2)	0.133
No. lesions treated	1 (1-2)	1 (1-2)	**0.029**
No. lesions treated ≥3, n (%)	154 (7.3)	78 (7.2)	0.993
Stent number	2 (1-2)	2 (1-3)	0.115
No. stents ≥3, n (%)	530 (25.0)	287 (26.6)	0.299
Type of drug-eluting stent			0.914
PES/SES, n (%)	945 (44.5)	477 (44.3)	
EES/ZES, n (%)	1179 (55.5)	600 (55.7)	
Minimum stent diameter, mm	2.75 (2.50-3.00)	2.75 (2.50-3.00)	**0.035**
Total stent length, mm	36 (23-56)	38 (24-60)	**0.047**
DAPT score	2 (1-2)	2 (1-2)	0.406
DAPT score≥2, n (%)	1175 (55.3)	585 (54.3)	0.590
Medications at discharge			
Aspirin, n (%)	2100 (98.9)	1065 (98.9)	0.968
$P2Y_{12}$ receptor inhibitor, n (%)	2097 (98.7)	1063 (98.7)	0.946
Oral anticoagulant, n (%)	4 (0.3)	2 (0.3)	1.000
β-blockers, n (%)	1944 (91.5)	995 (92.4)	0.401
Statins, n (%)	2040 (96.0)	1042 (96.8)	0.319
Calcium channel blockers, n (%)	984 (46.3)	509 (47.3)	0.617

Antiplatelet drugs at 6 months	n=2124	n=1077	
Aspirin, n (%)	2117 (99.7)	1075 (99.8)	0.727
$P2Y_{12}$ receptor inhibitor, n (%)	2116 (99.6)	1073 (99.6)	1.000
Antiplatelet drugs at 12 months	n=2124	n=1077	
Aspirin, n (%)	2106 (99.2)	1063 (98.7)	0.224
$P2Y_{12}$ receptor inhibitor, n (%)	2077 (97.8)	1051 (97.6)	0.718
Antiplatelet drugs at 18 months	n=2119	n=1077	
Aspirin, n (%)	2072 (97.8)	1054 (97.9)	0.880
$P2Y_{12}$ receptor inhibitor, n (%)	1409 (66.5)	735 (68.2)	0.319
Antiplatelet drugs at 24 months	n=2111	n=1075	
Aspirin, n (%)	2035 (96.4)	1043 (97.0)	0.358
$P2Y_{12}$ receptor inhibitor, n (%)	642 (30.4)	346 (32.2)	0.306
Antiplatelet drugs at 30 months	n=833	n=435	
Aspirin, n (%)	794 (95.3)	419 (96.3)	0.405
$P2Y_{12}$ receptor inhibitor, n (%)	188 (22.6)	130 (29.9)	**0.004**

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; EES, everolimus-eluting stent; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PES, paclitaxel-eluting stent; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; WBC, white blood cell; ZES, zotarolimus-eluting stent.

Table S2. Two-year clinical outcomes according to Lp(a) levels.

Clinical endpoint	No. patients with event, n(%)		Crude HR (95% CI)	Multivariable adjusted HR(95% CI)	IPTW adjusted HR(95% CI)
	Lp(a) ≤30mg/dl	Lp(a) >30mg/dl			
All-cause death/MI/stroke	30 (1.4)	28 (2.6)	**1.814 (1.083-3.036)**	**1.733 (1.023-2.934)**	**1.695 (1.005-2.860)**
All-cause death	9 (0.4)	9 (0.8)	1.969 (0.782-4.961)	1.974 (0.772-5.046)	1.772 (0.697-4.508)
Cardiac death	4 (0.2)	6 (0.6)	2.955 (0.834-10.473)	2.967 (0.816-10.785)	2.643 (0.738-9.459)
Non-fatal MI	8 (0.4)	10 (0.9)	2.443 (0.964-6.191)	2.434 (0.947-6.255)	2.370 (0.923-6.086)
Stroke	16 (0.8)	13 (1.2)	1.558 (0.749-3.240)	1.412 (0.659-3.023)	1.541 (0.727-3.263)
Definite/probable ST	5 (0.2)	8 (0.7)	**3.109 (1.017-9.505)**	**3.297 (1.060-10.251)**	**3.157 (1.015-9.822)**
BARC type 2, 3, or 5 bleeding	21 (1.0)	15 (1.4)	1.364 (0.703-2.647)	1.355 (0.680-2.698)	1.290 (0.661-2.514)

Variables included in Cox multivariable model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous stroke, peripheral vascular disease, low-density lipoprotein cholesterol, SYNTAX score, total lesion length, bifurcation lesion, minimum stent diameter, total stent length, and use of statin at discharge. Variables included in IPTW model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous percutaneous coronary intervention, previous stroke, peripheral vascular disease, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein cholesterol, total lesion length, type B2 or C lesion, chronic total occlusion, bifurcation lesion, number of lesions treated, stent number, use of everolimus- or zotarolimus-eluting stent, and use of β-blocker and statin at discharge. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; ST, stent thrombosis.

Table S3. Two-year clinical outcomes according to Lp(a) levels and DAPT duration.

Clinical endpoint	DAPT ≤ 1year, n(%)	DAPT > 1year, n(%)	P value	Crude HR (95% CI)	Multivariable adjusted HR(95% CI)	IPTW adjusted HR(95% CI)
All-cause death/MI/stroke						
Lp(a) ≤ 30mg/dl	10 (1.6)	20 (1.3)	0.566	0.769 (0.359-1.644)	0.775 (0.356-1.687)	0.705 (0.331-1.503)
Lp(a) > 30mg/dl	**13 (4.5)**	**15 (1.9)**	**0.020**	**0.407 (0.193-0.856)**	**0.344 (0.159-0.744)**	**0.351 (0.164-0.751)**
All-cause death						
Lp(a) ≤ 30mg/dl	**7 (1.2)**	**2 (0.1)**	**0.003**	**0.114 (0.024-0.550)**	**0.092 (0.017-0.485)**	**0.095 (0.020-0.460)**
Lp(a) > 30mg/dl	**9 (3.1)**	**0 (0)**	**< 0.001**	NA	NA	NA
Cardiac death						
Lp(a) ≤ 30mg/dl	**4 (0.7)**	**0 (0)**	**0.007**	NA	NA	NA
Lp(a) > 30mg/dl	**6 (2.1)**	**0 (0)**	**< 0.001**	NA	NA	NA
Non-fatal MI						
Lp(a) ≤ 30mg/dl	1 (0.2)	7(0.5)	0.452	2.758 (0.339-22.420)	3.218 (0.375-27.601)	2.656 (0.329-21.412)
Lp(a) > 30mg/dl	4 (1.4)	6 (0.8)	0.473	0.540 (0.152-1.914)	0.541 (0.150-1.952)	0.386 (0.102-1.459)
Stroke						
Lp(a) ≤ 30mg/dl	4 (0.7)	12 (0.8)	1.000	1.129 (0.363-3.510)	1.129 (0.352-3.627)	1.026 (0.332-3.177)
Lp(a) > 30mg/dl	3 (1.0)	10 (1.3)	1.000	1.162 (0.319-4.233)	0.856 (0.221-3.318)	1.058 (0.286-3.920)
Definite/probable ST						
Lp(a) ≤ 30mg/dl	3 (0.5)	2 (0.1)	0.145	0.267 (0.045-1.599)	0.142 (0.017-1.165)	0.246 (0.041-1.472)
Lp(a) > 30mg/dl	**6 (2.1)**	**2 (0.3)**	**0.006**	**0.120 (0.024-0.595)**	**0.099 (0.019-0.512)**	**0.092 (0.018-0.469)**
BARC type 2, 3, or 5 bleeding						
Lp(a) ≤ 30mg/dl	3 (0.5)	18 (1.2)	0.144	2.284 (0.672-7.766)	2.249 (0.658-7.689)	2.314 (0.672-7.967)
Lp(a) > 30mg/dl	3 (1.0)	12 (1.5)	0.771	1.343 (0.378-4.775)	1.172 (0.318-4.321)	1.165 (0.317-4.284)

Variables included in Cox multivariable model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous stroke, peripheral vascular disease, low-density lipoprotein cholesterol, SYNTAX score, total lesion length, bifurcation lesion, minimum stent diameter, total stent length, and use of statin at

discharge. Variables included in IPTW model were age, sex, body mass index, current smoker, diabetes, hypertension, dyslipidemia, previous MI, previous percutaneous coronary intervention, previous stroke, peripheral vascular disease, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein cholesterol, total lesion length, type B2 or C lesion, chronic total occlusion, bifurcation lesion, number of lesions treated, stent number, use of everolimus- or zotarolimus-eluting stent, and use of β-blocker and statin at discharge. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; ST, stent thrombosis.

Figure S1. Absolute standard difference before and after inverse probability of treatment weighting analysis between the DAPT >1-year and DAPT ≤1-year groups. COPD, chronic obstructive pulmonary disease; EES, everolimus-eluting stent; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; ZES, zotarolimus-eluting stent.

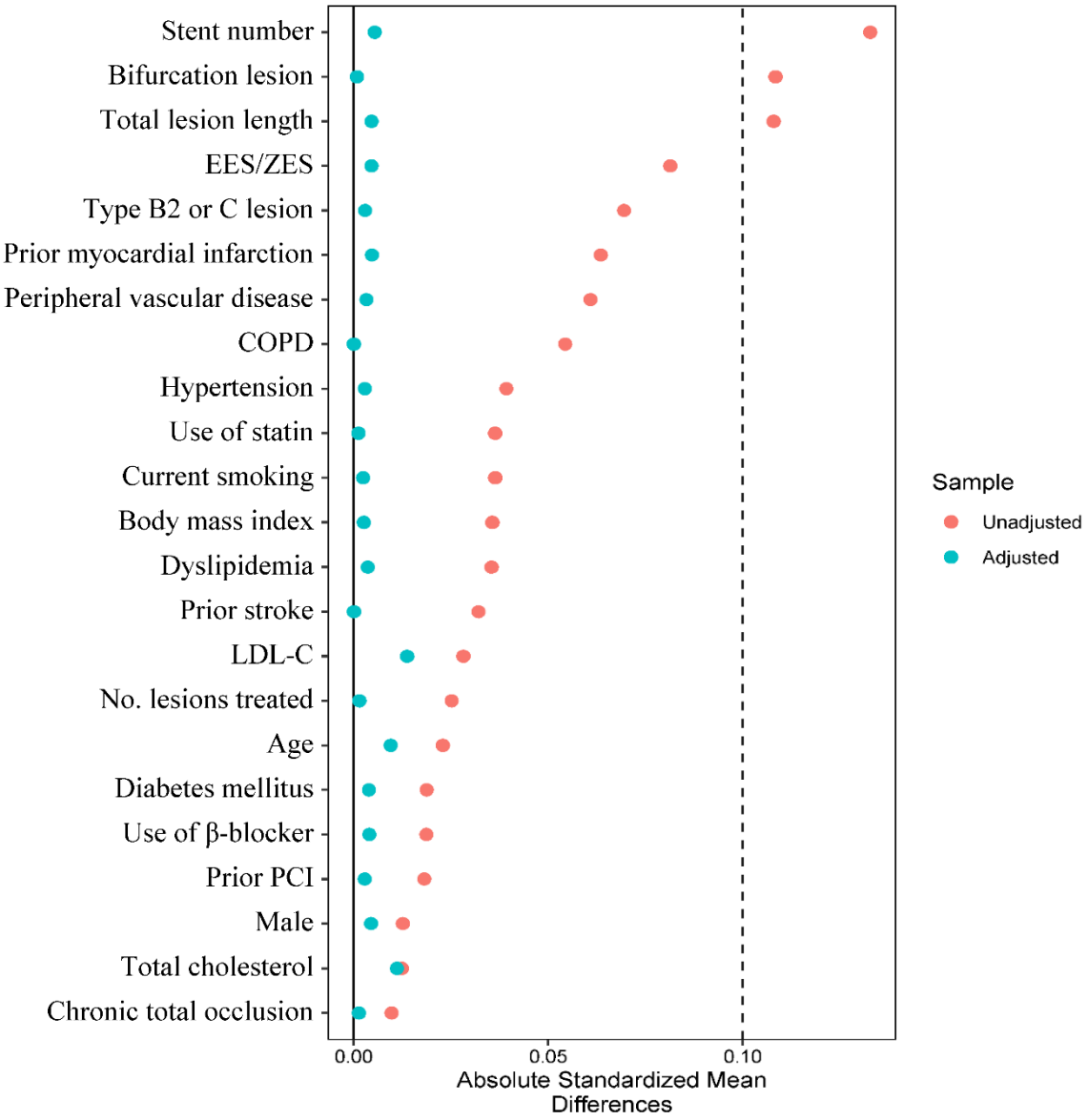

Figure S2. Side-by-side boxplots before and after inverse probability of treatment weighting analysis between the DAPT >1-year and DAPT ≤1-year groups. IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.

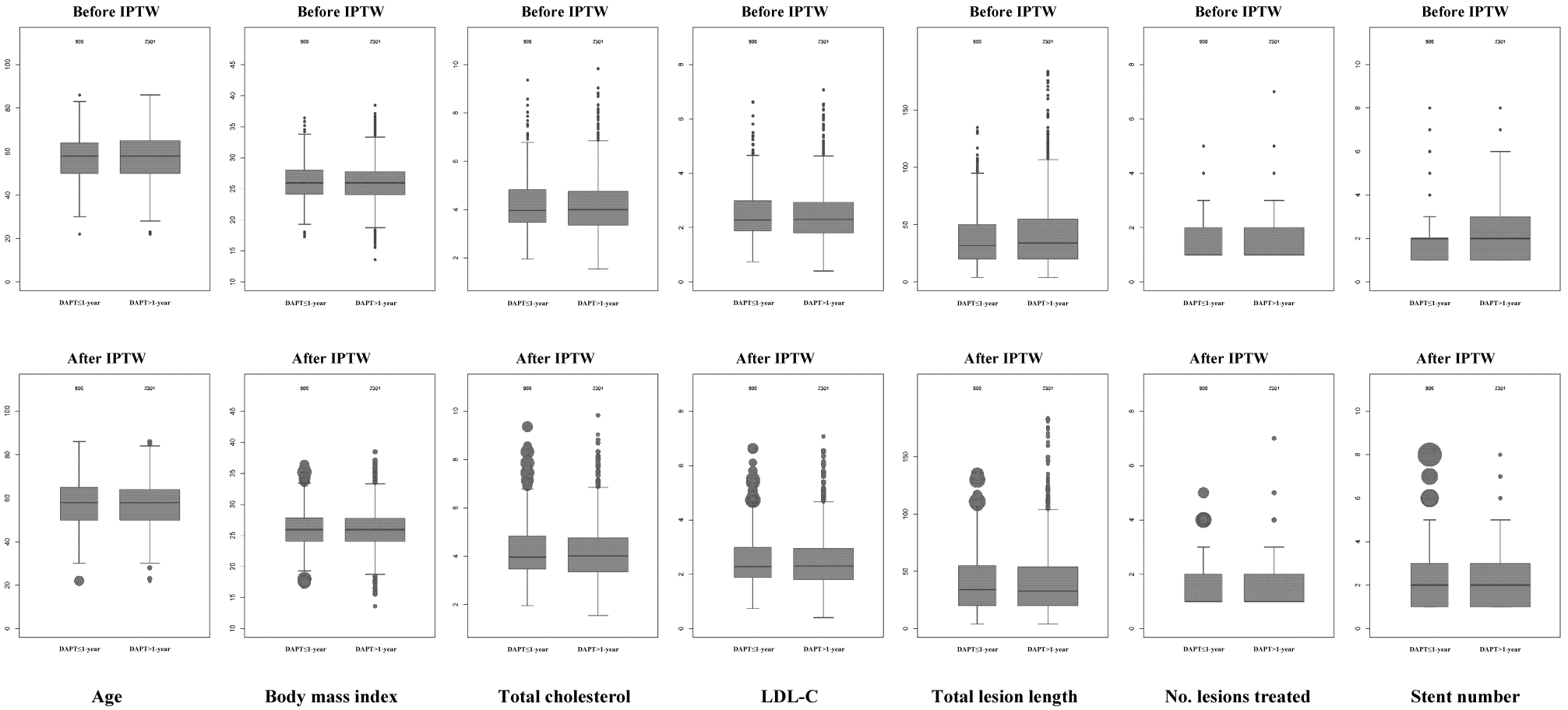

Figure S3. Kaplan–Meier curves for 2.5-year clinical outcomes according to Lp(a) levels (>30mg/dl vs. ≤30mg/dl). BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; ST, stent thrombosis.

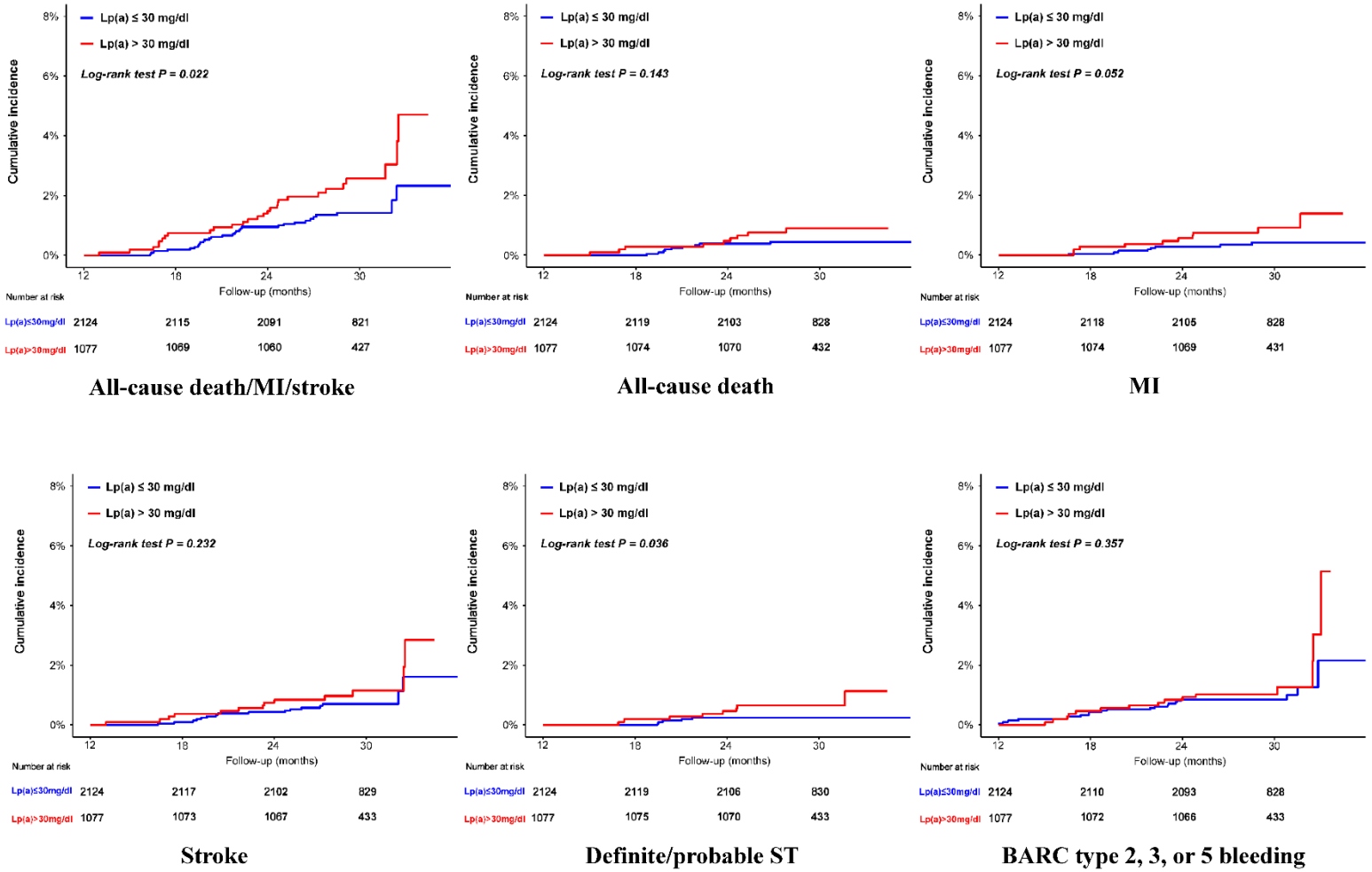

Figure S4. Absolute standard difference before and after inverse probability of treatment weighting analysis between the Lp(a) levels >30mg/dl and Lp(a) levels ≤30mg/dl groups. COPD, chronic obstructive pulmonary disease; EES, everolimus-eluting stent; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; ZES, zotarolimus-eluting stent.

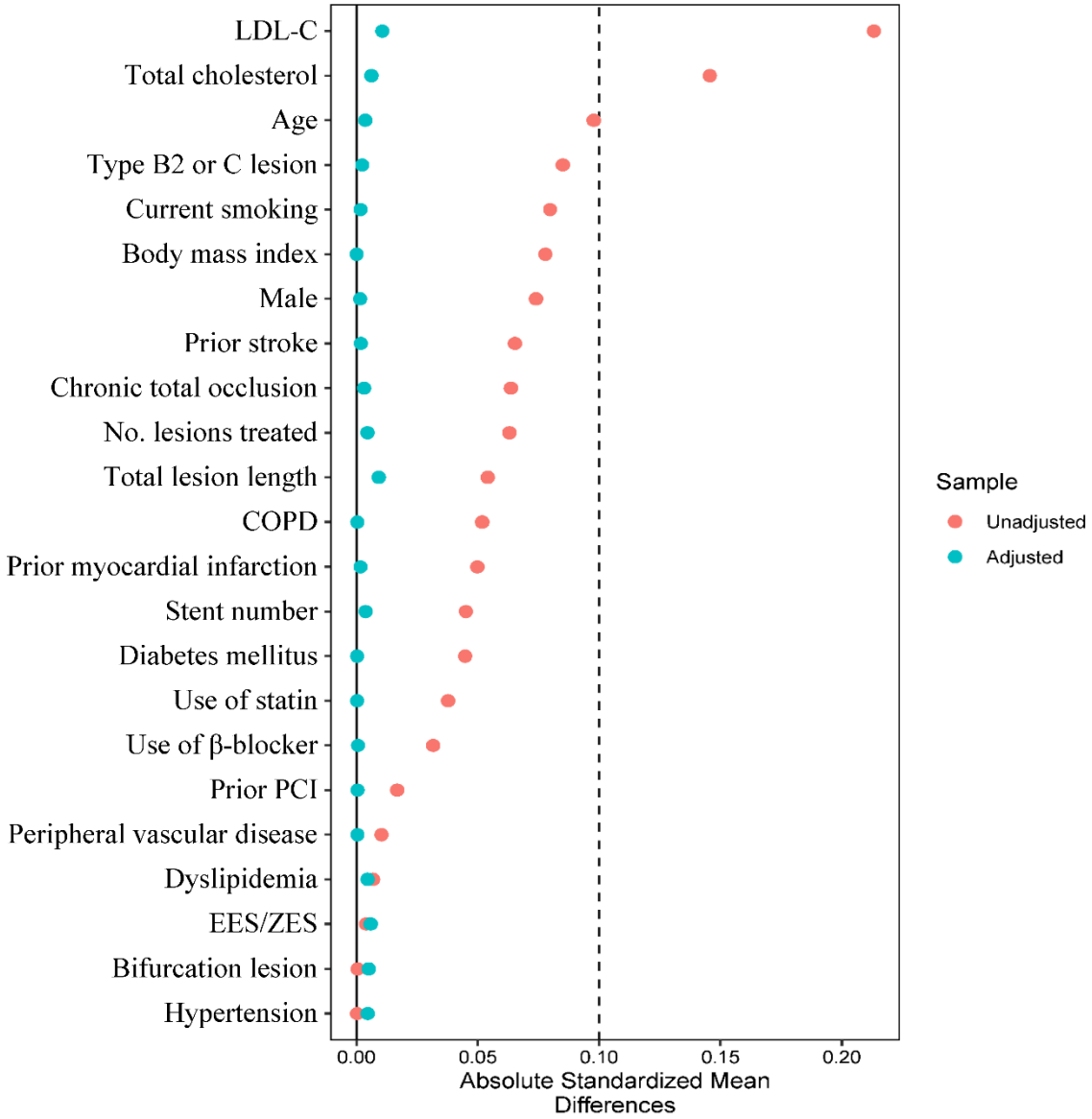

Figure S5 Side-by-side boxplots before and after inverse probability of treatment weighting analysis between the Lp(a) levels >30mg/dl and Lp(a) levels ≤30mg/dl groups. IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.

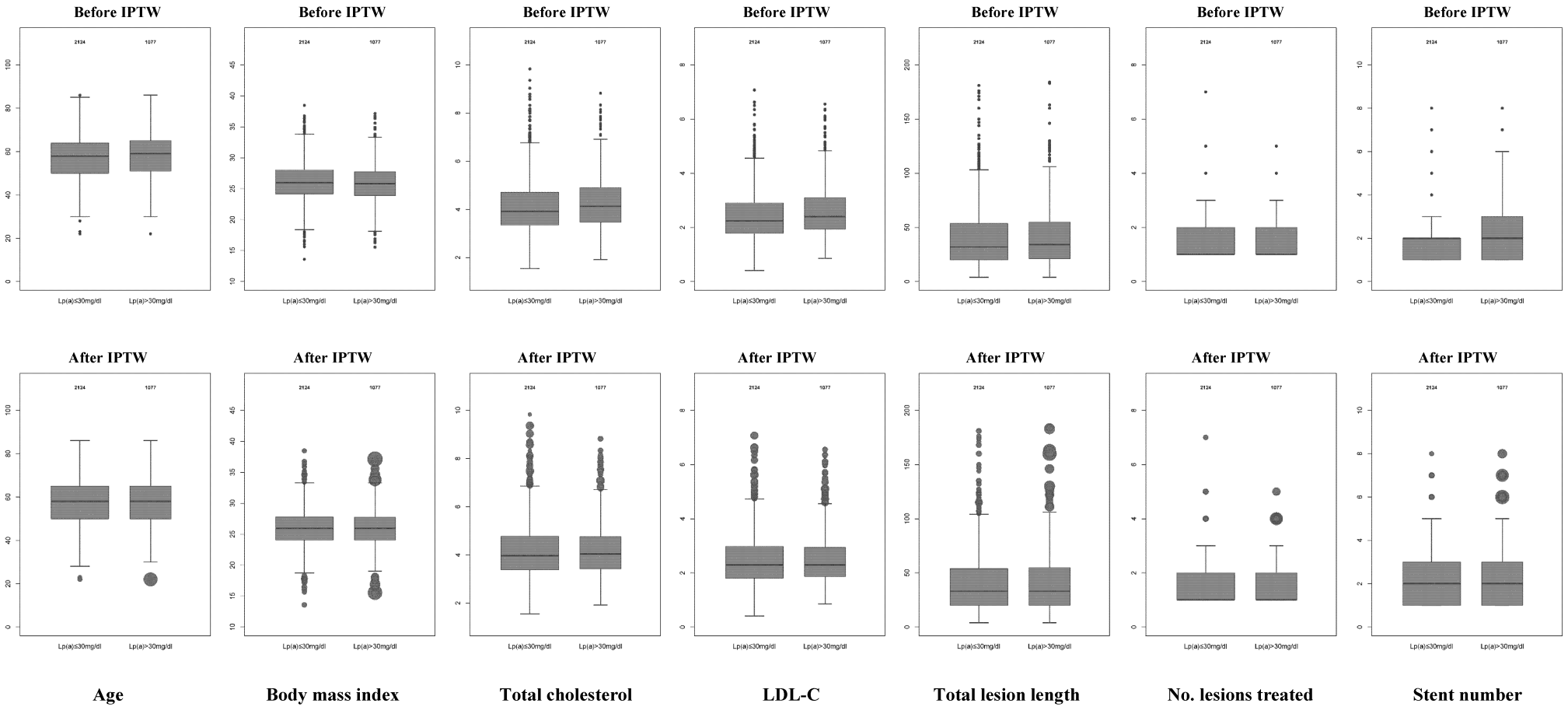

Figure S6. Side-by-side boxplots before and after inverse probability of treatment weighting analysis between the DAPT >1-year and DAPT ≤1-year groups in patients with Lp(a) levels >30mg/dl. IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.

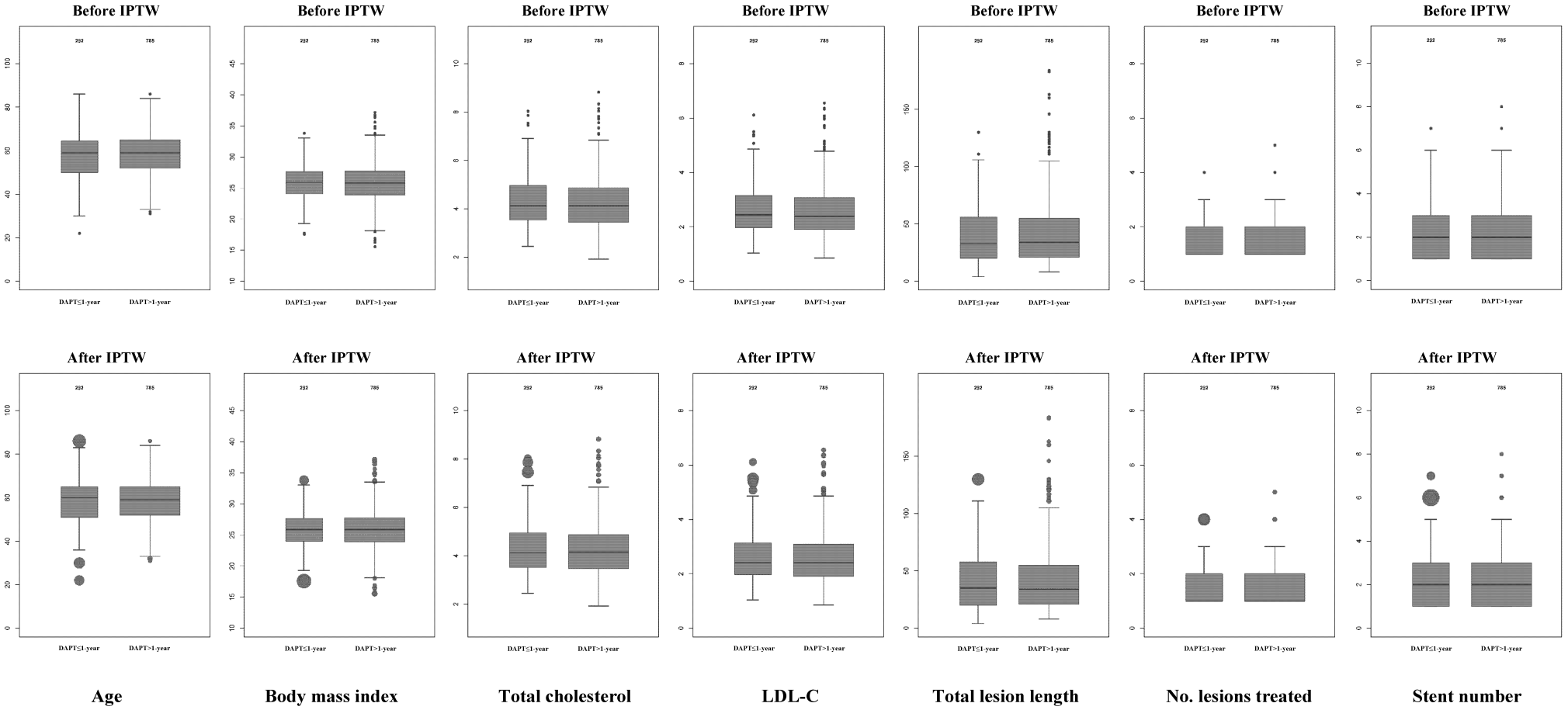

Figure S7. Side-by-side boxplots before and after inverse probability of treatment weighting analysis between the DAPT >1-year and DAPT ≤1-year groups in patients with Lp(a) levels ≤30mg/dl. IPTW, inverse probability of treatment weighting; LDL-C, low-density lipoprotein cholesterol.