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
Elevated Lp(a) (lipoprotein(a)) is one of the most common genetic lipid disorders, affecting 20% to 30% of the population worldwide. Over the past decade, Lp(a) has been shown to be an independent and causal risk factor for cardiovascular disease. Moreover, increasing evidence supports that Lp(a) levels play an important role in predicting subsequent ischemic events in patients with coronary artery disease (CAD). 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. 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-LRx (apolipoprotein A-LRx), 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.

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, 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.

**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.

**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. 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]). 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. 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%. 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. 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. 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. Bleeding events were categorized on the basis of the Bleeding Academic Research Consortium classifications. 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 χ² 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. 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.
| 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/m²                        | 26.0 (24.1–28.0) | 26.0 (24.0–27.8)  | 0.357   |
| Current smoker, n (%)                         | 520 (57.8)       | 1298 (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, 10³/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)  | 18.8 (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)
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%),
| Variable                                      | Lp(a) ≤30 mg/dL, n=2124 | Lp(a) >30 mg/dL, n=1077 | P value | Lp(a) ≤30 mg/dL, n=608 | Lp(a) >30 mg/dL, n=1516 | P value | Lp(a) ≤30 mg/dL, n=292 | Lp(a) >30 mg/dL, 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/m²                       | 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)                | 0.314   | 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 (%)                | 32 (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   |                           |                           |         |
| SYNTAX score                                 | 9 (6–17)                 | 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   |                           |                           |         |
| Laboratory data                              |                          |                          |         |                          |                          |         |                          |                          |         |
| WBC, 10³/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   |                           |                           |         |
| HDL-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 (6–18)                 | 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   |                           |                           |         |

(Continued)
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 statistically 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 2. Continued

| Variable                              | 
|---------------------------------------|
| Lp(a) ≤30 mg/dL, n=2124               |
| DAPT ≤1 y, n=608                      | DAPT >1 y, n=1516 | 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 |
| P2Y12 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)           | 0.845 |
| 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 (44.8)         | 713 (47.0)        | 0.304 | 134 (45.9)         | 375 (47.8)        | 0.583 |

| Antiplatelet drugs at 6 mo            |
|---------------------------------------|
| Aspirin, n (%)                        | 601 (98.8)         | 1516 (100)        | <0.001 | 290 (99.3)         | 785 (100)         | 0.073 |
| P2Y12 receptor inhibitor, n (%)       | 600 (98.7)         | 1516 (100)        | <0.001 | 278 (95.2)         | 785 (100)         | <0.001 |

| Antiplatelet drugs at 12 mo           |
|---------------------------------------|
| Aspirin, n (%)                        | 590 (97.0)         | 1516 (100)        | <0.001 | 278 (95.2)         | 785 (100)         | <0.001 |
| P2Y12 receptor inhibitor, n (%)       | 561 (92.3)         | 1516 (100)        | <0.001 | 266 (91.1)         | 785 (100)         | <0.001 |

| Antiplatelet drugs at 18 mo           |
|---------------------------------------|
| Aspirin, n (%)                        | 563 (92.8)         | 1509 (99.8)       | <0.001 | 270 (92.5)         | 784 (99.9)        | <0.001 |
| P2Y12 receptor inhibitor, n (%)       | 16 (2.6)           | 1393 (92.1)       | <0.001 | 8 (2.7)            | 727 (92.6)        | <0.001 |

| Antiplatelet drugs at 24 mo           |
|---------------------------------------|
| Aspirin, n (%)                        | 560 (92.3)         | 1475 (98.1)       | <0.001 | 270 (92.5)         | 773 (98.7)        | <0.001 |
| P2Y12 receptor inhibitor, n (%)       | 16 (2.6)           | 626 (41.6)        | <0.001 | 6 (2.1)            | 340 (43.4)        | <0.001 |

| Mean DAPT time, d                     |
|---------------------------------------|
| Aspirin, n (%)                        | 145 (87.9)         | 649 (97.2)        | 0.003 | 83 (88.3)          | 336 (97.6)        | <0.001 |
| P2Y12 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 |

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.
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, 0.016–0.469]) 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. Since then, a growing body of evidence from meta-analyses, Mendelian randomization studies, and genome-wide association studies 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. 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]). 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.

| Clinical end point | No. patients with event, n (%) | Crude HR (95% CI) | Multivariable adjusted HR (95% CI) | IPTW adjusted HR (95% CI) |
|-------------------|-------------------------------|-----------------|-----------------------------------|-------------------------|
| All-cause death/ MI/stroke | 23 (2.6) 35 (1.5) | 0.566 (0.334–0.998) | 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 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 applicable; ST, stent thrombosis; and SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.
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-LRx, 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-LRx 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 P2Y12 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 who received DAPT for 6 to 12 months or >12 months after PCI with a DES. In contrast, prolonged DAPT was not significantly

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.
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.
Elevated Lipoprotein(a), PCI, and Prolonged DAPT

Cui et al. Elevated Lipoprotein(a), PCI, and Prolonged DAPT

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 P2Y12 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 (2021-12 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;102:1062–1065. doi: 10.1161/01.CIR.102.10.1062
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, Pedersen JF, Hopewell JC, Kyrilaku 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 heart disease. N Engl J Med. 2009;361:2518–2528. doi: 10.1056/NEJMoa0902604
5. Collaboration ERF, Erquu S, Kaptego 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 QI, Li X, Feng Q, Kubo M, Kullo IJ, Peissig PL, Karlsson EW, JarvP 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, Tsikinas S, Sloan S, Ren AF, Hoffman EB, Desai NR, Solomon SD, Domanski M, Ariai 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, Miyazaki C, Sonoda T, Konishi H, Tsuibo 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. Willett P, Ridker PM, Nestel PJ, Simons 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)31562-0
12. Liu H-H, Cao YX, Jin J-L, Zhang H-W, Hua QI, Li Y-F, Guo Y-L, Zhu C-G, Wu N-Q, Xu RX, 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, Weerakody G, Riesmeyer JS, Nicholas 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:e622–e624. doi: 10.2337/dci19-1117
14. Tsikinas S, Karwatowska-Prokopczuk E, Gouri-Berthoud I, Tardif JC, Baun 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/NEJMoa1905299
15. Tsikinas 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. Tsikinas 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.cjc.2019.02.017
18. Wang HY, Cai ZX, Yin D, Song WH, Feng L, Gao RL, Yang YJ, Dou KF. Optimal strategy for antplatelet 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, Sriratana H, Fileman K, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020;382:1396–1407. 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 WW, Dong YG, et al. 2016 Chinese guideline for the management of dyslipidemia in adults. Chin J Cardiol. 2016;44:833–853.
22. Anderson TJ, Grøgør J, Raaschou-Nielsen O, Barter PJ, Cuthbertson B, Dawes RG, Francis GA, Genest J Jr, Gropper 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 GA, Gabriel Stieg P, Morel M-A, Mauri L, Vanckx P, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.655313
25. Mehran R, Rao SV, Bhatt DL, Gibson CM, Calveta 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, Bitner VA, Aylward P, Baccara-Dinet M, Bhatt DL, Diaz R, Fras Z, Goodman SG, Halvorsen S, Harrington RA, et al. Lipoprotein(a) lowering by
allrocumab 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, Willett 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/ jamacardi.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.
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/m²            | 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 CAGB, 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   |
| Feature                      | Group 1          | Group 2          | p-value |
|------------------------------|------------------|------------------|---------|
| 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   |
| Time          | n= | Aspirin, n (%) | P2Y$_{12}$ receptor inhibitor, n (%) | p-value |
|--------------|----|---------------|-------------------------------------|---------|
| 6 months     | 2124  | 2117 (99.7)   | 2116 (99.6)                        | 0.727   |
|              | 1077  | 1075 (99.8)   | 1073 (99.6)                        |         |
| 12 months    | 2124  | 2106 (99.2)   | 2077 (97.8)                        | 0.224   |
|              | 1077  | 1063 (98.7)   | 1051 (97.6)                        |         |
| 18 months    | 2119  | 2072 (97.8)   | 1409 (66.5)                        | 0.880   |
|              | 1077  | 1054 (97.9)   | 735 (68.2)                         |         |
| 24 months    | 2111  | 2035 (96.4)   | 642 (30.4)                         | 0.358   |
|              | 1075  | 1043 (97.0)   | 346 (32.2)                         |         |
| 30 months    | 833   | 794 (95.3)    | 188 (22.6)                         | 0.004   |
|              | 435   | 419 (96.3)    | 130 (29.9)                         |         |

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.
| 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.
| Clinical endpoint | DAPT ≤ 1 year, n(%) | DAPT > 1 year, 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                        |
| 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                        |
| 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...
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.