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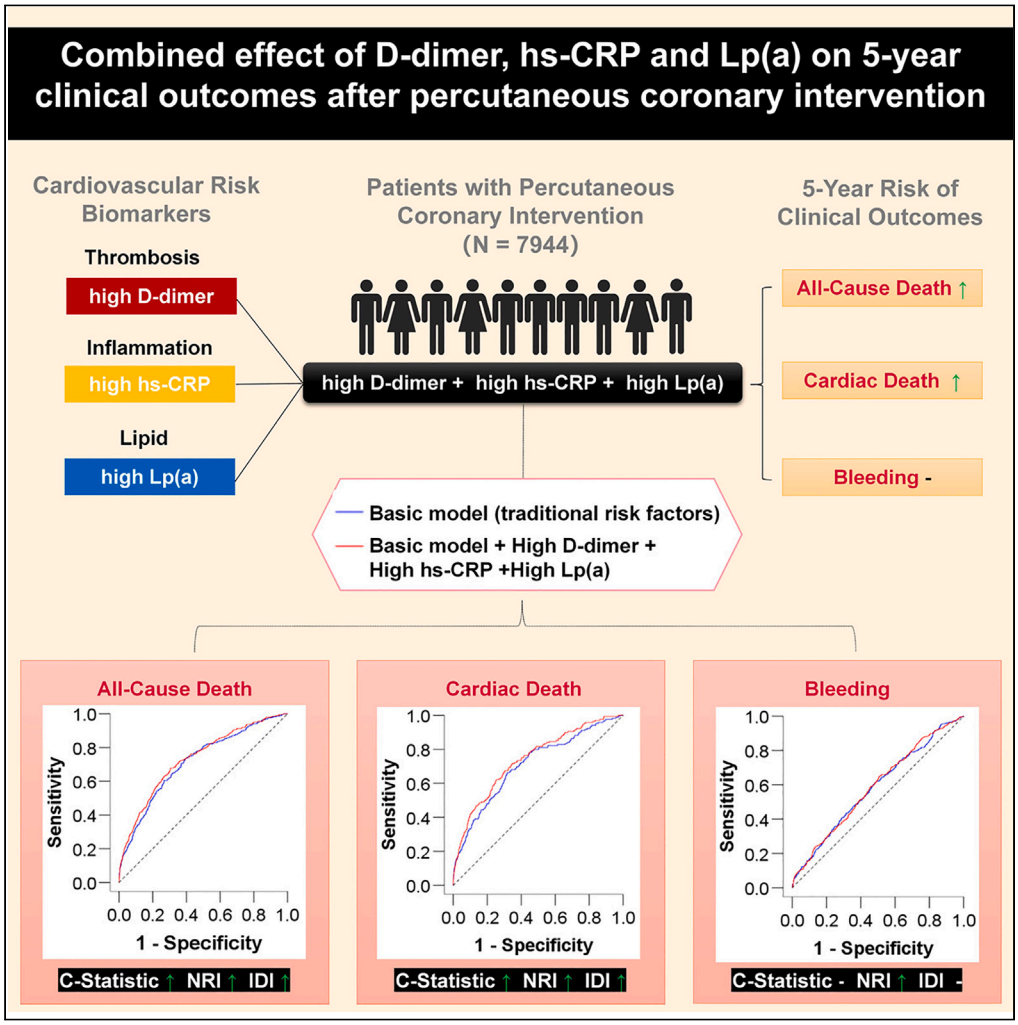

Jiawen Li, Pei Zhu, Xiaofang Tang, ..., Bo Xu, Jinqing Yuan, Xueyan Zhao

zhao_xueyan@sina.com (X.Z.)
jqyuanfw@163.com (J.Y.)

Highlights

Combined elevated D-dimer, hs-CRP, and Lp(a) intensified ischemic adverse effect

These biomarkers combination had incremental value beyond traditional risk factors

Concomitantly monitoring these biomarkers may help to identify the high-risk patients

Li et al., iScience 26, 107030
July 21, 2023 © 2023
https://doi.org/10.1016/j.isci.2023.107030

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Combined effect of D-dimer, hs-CRP, and Lp(a) on 5-year clinical outcomes after percutaneous coronary intervention: A large real-world study in China

Jiawen Li,[1] Pei Zhu,[1] Xiaofang Tang,[1] Lin Jiang,[1] Yulong Li,[1] Kailun Yan,[1] Weixian Yang,[1] Shubin Qiao,[1] Yuejin Yang,[1] Runlin Gao,[1] Bo Xu,[1] Jinqing Yuan,[1,*] and Xueyan Zhao[1,2,*]

SUMMARY

To reduce cardiovascular risk in patients with established coronary heart disease, the present study investigated the combined effect of D-dimer, high-sensitivity C-reactive protein (hs-CRP), and lipoprotein(a) [Lp(a)] on long-term cardiovascular outcomes from the perspectives of thrombosis, inflammation, and lipid risk simultaneously. Consecutive 10,724 patients with percutaneous coronary intervention (PCI) were enrolled throughout 2013. Over a median follow-up of 5.1 years, each individual elevation of D-dimer, hs-CRP, and Lp(a) was associated with poor ischemic outcomes but not bleeding. Concurrent high D-dimer, hs-CRP, and Lp(a) had even greater risks of all-cause death (hazard ratio [HR] 2.714, 95% confidence interval [CI] 1.742–4.231) and cardiac death (HR 4.152, 95% CI 2.207–7.812) and had incremental value beyond the traditional risk factors model. Concurrent high D-dimer, hs-CRP, and Lp(a) levels had a synergistic effect on adverse 5-year ischemic outcomes, highlighting that the potential utility of simultaneous assessment of multiple cardiovascular risk biomarkers may help to identify high-risk patients after PCI.

INTRODUCTION

Despite the fact that, in recent years, increasing patients with coronary heart disease (CHD) have received comprehensive treatment recommended by guidelines, including percutaneous coronary intervention (PCI), antiplatelet therapy, and intensive lipid-lowering therapy, their long-term risk of death and cardiovascular events remains unacceptably high.[1] Consequently, managing cardiovascular risk in secondary prevention populations has become a hotly debated topic. Meanwhile, determining high-risk patients with established CHD who are at risk of recurrent events has also been a challenging problem.[2] In addition to traditional risk factors, thrombotic risk, inflammatory risk, and lipid risk are all critical determinants of the recurrence of ischemic events in patients with CHD.[3–5] Previous studies have shown that the concentrations of D-dimer, high-sensitivity C-reactive protein (hs-CRP), and lipoprotein(a) [Lp(a)] reflect the degree of above cardiovascular risks.[6–8] These biomarkers are not only related to the severity of coronary artery[9–11] but are also independent risk factors for all-cause death in patients with PCI.[12–14]

The latest research has demonstrated that there existed complex interactions between lipid risk and inflammation risk, and the co-occurrence of these two factors can synergistically potentiate the adverse effects.[15,16] Furthermore, in our previous studies[12] and many large-scale studies,[6,17] D-dimer has emerged as a novel biomarker to evaluate the thrombotic risk of CHD. Hence, we undertook this study from the perspectives of thrombosis, inflammation, and lipid risk at the same time to examine the combined effect of D-dimer, hs-CRP, and Lp(a) on 5-year clinical outcomes. Moreover, we sought to assess whether the incorporation of these three cardiovascular risk biomarkers (D-dimer, hs-CRP, and Lp(a)) would help to improve the predictive value of a basic model established with traditional risk factors using a large-scale real-world cohort of patients with PCI.

RESULTS

Baseline characteristics

The study included a total of 7,944 eligible patients finally, as depicted in Figure 1. The mean age of the patients was 58.4 ± 10.3 years, and 6,067 (76.4%) were men. Of the total, 4,751 (59.8%) patients had

[1]Department of Cardiology, Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

[2]Lead contact

*Correspondence: zhao_xueyan@sina.com (X.Z.), jqyuanfw@163.com (J.Y.)

https://doi.org/10.1016/j.isci.2023.107030

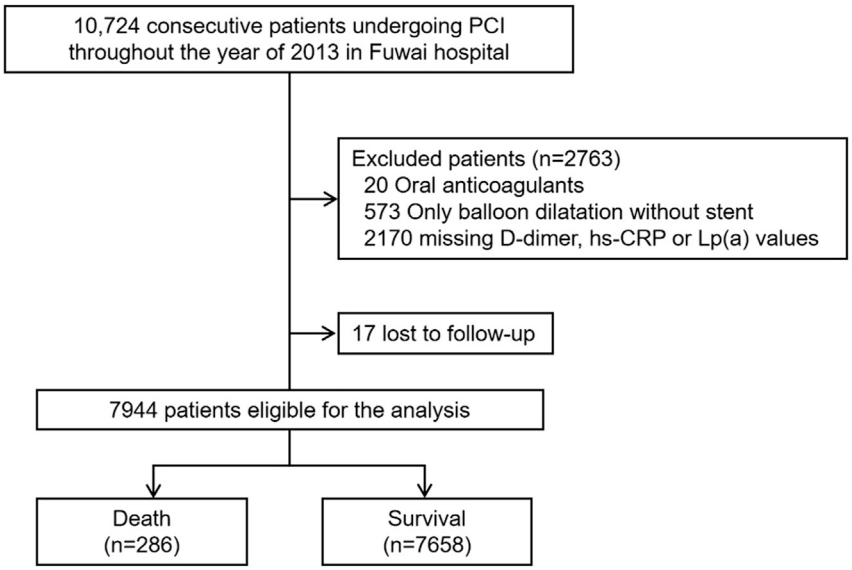


Figure 1. The flowchart of the study

PCI, percutaneous coronary intervention; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a).

acute coronary syndrome (ACS), including acute myocardial infarction and unstable angina pectoris, and 3,193 (40.2%) had stable angina pectoris (SAP). Baseline characteristics of patients with all-cause death versus patients who survived are presented in Table 1. Patients with all-cause death were older and had a lower body mass index (BMI), more past medical history (previous PCI, previous coronary artery bypass grafting [CABG]), hypertension, diabetes, chronic obstructive pulmonary disease [COPD], peripheral artery disease [PAD], previous stroke, and previous myocardial infarction), a lower left ventricular ejection fraction, a higher predicting bleeding complications in patients undergoing stent implantation and subsequent dualantiplatelet therapy (PRECISE-DAPT) score, a lower hemoglobin, a higher white blood cell count, a lower estimated glomerular filtration rate, a higher D-dimer, a higher hs-CRP, and a higher Lp(a) than those who survived (Table 1). The distributions of D-dimer (0.28 μg/mL fibrinogen-equivalent unit [FEU], interquartile range [IQR]: 0.20–0.41 μg/mL), hs-CRP (1.60 mg/L, IQR: 0.78–3.66 mg/L), and Lp(a) (18.53 mg/dL, IQR: 7.95–41.09 mg/dL) are illustrated in Figure S1. Baseline characteristics of high D-dimer versus low D-dimer, high hs-CRP versus low hs-CRP, and high Lp(a) versus low Lp(a) are shown in Tables S1–S3, respectively.

Individual cardiovascular risk biomarkers and clinical outcomes

Over a median follow-up of 5.1 years (IQR 5.0–5.1), 286 (3.6%) all-cause death, 169 (2.1%) cardiac death, and 335 (4.2%) bleeding occurred. Patients were stratified into two groups according to individual D-dimer, individual hs-CRP, and individual Lp(a) levels. The incidences of all-cause death and cardiac death were higher in high D-dimer versus low D-dimer (Figure 2A), in high hs-CRP versus low hs-CRP (Figure 2B), and in high Lp(a) versus low Lp(a) (Figure 2C). The Kaplan-Meier estimates showed that those with individually high levels of D-dimer, hs-CRP, or Lp(a) had higher all-cause death rates (all Log rank $p < 0.05$, Figures 3A–3C), which were consistent with the results from multivariate Cox analysis in Table 2.

In multivariable adjustment Cox analysis, high D-dimer, high hs-CRP, and high Lp(a) were independently associated with the increased risks of all-cause death (HR: 1.922, [95% CI: 1.464–2.522]; HR: 1.290, [95% CI: 1.014–1.641]; HR: 1.409, [95% CI: 1.114–1.783], respectively) and cardiac death (HR: 2.065, [95% CI: 1.443–2.955]; HR: 1.441, [95% CI: 1.051–1.977]; HR: 1.796, [95% CI: 1.326–2.434], respectively) (Table 2). Multivariable adjusted restricted cubic spline analyses showed the linear association of D-dimer, hs-CRP, and Lp(a) levels with all-cause death (all $p < 0.05$; Figures S2A–S2C) and the nonlinear relationship of D-dimer with all-cause death ($p < 0.001$; Figure S2A).

Table 1. Baseline characteristics of patients stratified by the primary endpoint

Variables	Total Population (N = 7,944)	All-cause Death (N = 286)	Survival (N = 7,658)	p Value
Demographics				
Age, years	58.4 ± 10.3	65.6 ± 10.4	58.2 ± 10.2	<0.001
Men	6,067 (76.4)	220 (76.9)	5,847 (76.4)	0.823
BMI, kg/m^2	25.9 ± 3.2	25.5 ± 3.2	25.9 ± 3.2	0.038
Cardiovascular Risk Factor				
Previous PCI	1,912 (24.1)	86 (30.1)	1,826 (23.8)	0.016
Previous CABG	323 (4.1)	21 (7.3)	302 (3.9)	0.004
Hypertension	5,083 (64.0)	286 (74.5)	4,870 (63.6)	<0.001
Diabetes	2,404 (30.3)	106 (37.1)	2,298 (30.0)	0.011
COPD	190 (2.4)	17 (5.9)	173 (2.3)	<0.001
PAD	213 (2.7)	15 (5.2)	198 (2.6)	0.006
Previous Stroke	820 (10.3)	50 (17.5)	770 (10.1)	<0.001
Previous MI	1,449 (18.2)	71 (24.8)	1,378 (18.0)	0.003
Current/ever-smoker	4,589 (57.8)	173 (60.5)	4,416 (57.7)	0.342
Clinical Presentation				
ACS	4,751 (59.8)	170 (59.4)	4,581 (59.8)	0.898
SAP	3,193 (40.2)	116 (40.6)	3,077 (40.2)	
LVEF, %	63.0 ± 7.2	60.9 ± 9.3	63.0 ± 7.1	<0.001
PRECISE-DAPT Score[a]	9.9 ± 7.9	15.6 ± 10.7	9.7 ± 7.7	<0.001
Laboratory Results at Admission				
Hb, g/dL	14.4 ± 1.6	14.0 ± 1.7	14.4 ± 1.5	<0.001
WBC, 10^9/L	6.8 ± 2.0	7.2 ± 2.2	6.8 ± 2.0	0.007
eGFR, ml/min	91.4 ± 15.1	83.0 ± 19.3	91.7 ± 14.8	<0.001
LDL-C, mmol/L	2.5 ± 0.9	2.4 ± 0.9	2.5 ± 0.9	0.075
Procedural Presentation				
SYNTAX Score[b]	11.5 ± 8.0	12.0 ± 8.7	11.5 ± 8.0	0.276
Number of Stent	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.849
Femoral Artery Puncture	578 (7.3)	26 (9.1)	552 (7.2)	0.229

(*Continued on next page*)

Table 1. *Continued*

Variables	Total Population (N = 7,944)	All-cause Death (N = 286)	Survival (N = 7,658)	p Value
GPI	1,351 (17.0)	43 (15.0)	1,308 (17.1)	0.366
Medication at Discharge				
Aspirin	7,836 (98.6)	280 (97.9)	7,556 (98.7)	0.288
Clopidogrel	7,932 (99.8)	286 (100.0)	7,646 (99.8)	1.000
Statin	7,632 (96.1)	276 (96.5)	7,356 (96.1)	0.702
Beta-blocker	7,141 (89.9)	251 (87.8)	6,890 (90.0)	0.224
Cardiovascular Risk Biomarkers				
D-dimer, μg/mL FEU	0.28 (0.20–0.41)	0.38 (0.28–0.56)	0.28 (0.19–0.40)	<0.001
High D-dimer	3,890 (49.0)	208 (72.7)	3,682 (48.1)	<0.001
hs-CRP, mg/L	1.60 (0.78–3.66)	2.14 (1.03–5.46)	1.59 (0.78–3.59)	<0.001
High hs-CRP	3,373 (42.5)	148 (51.7)	3,225 (42.1)	0.001
Lp(a), mg/dL	18.53 (7.95–41.09)	22.45 (8.91–48.22)	18.41 (7.94–40.71)	<0.001
High Lp(a)	2,751 (34.6)	124 (43.3)	2,627 (34.3)	0.002

Values are mean ± standard deviation, median (IQR) or n (%).

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; SAP, stable angina pectoris; LVEF, left ventricular ejection fraction; Hb, hemoglobin; WBC: white blood cell count; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; GPI: glycoprotein IIb/IIIa inhibitor; FEU, fibrinogen-equivalent unit; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a).

[a]Calculated online (http://www.precisedaptscore.com).

[b]Calculated online (http://www.syntaxscore.com).

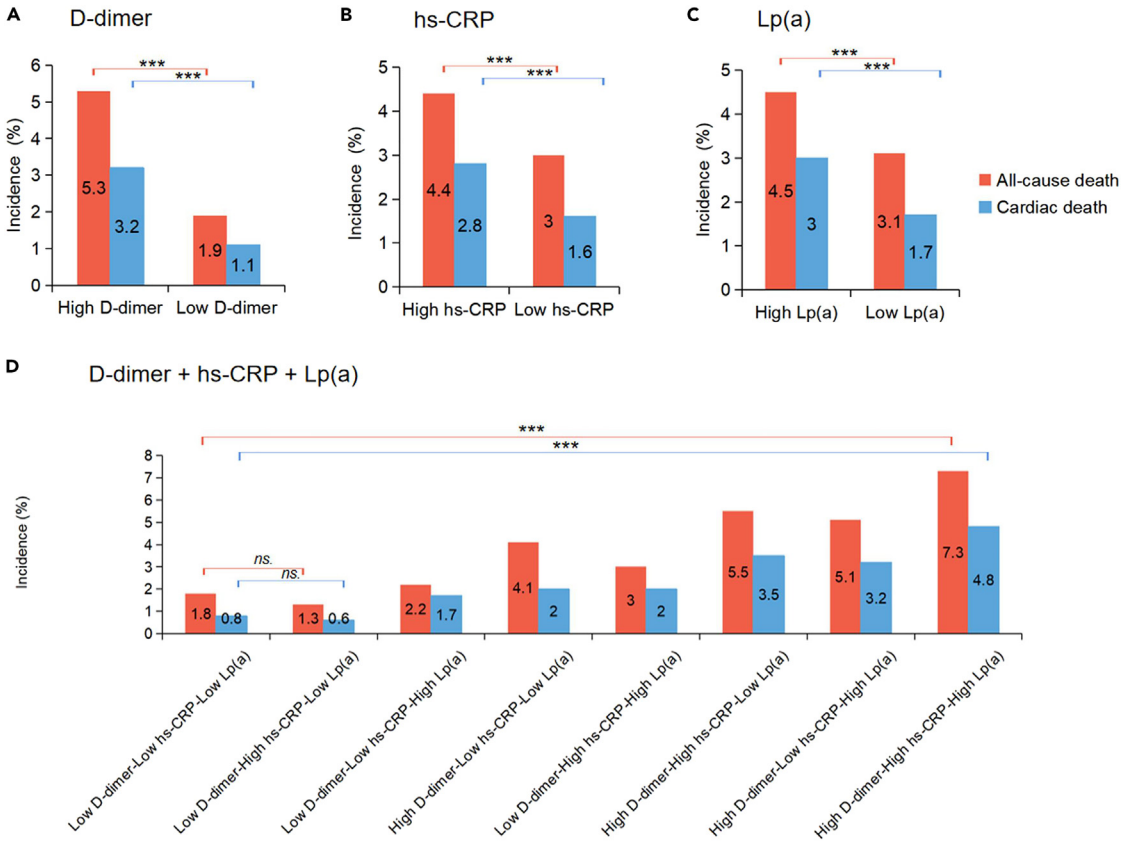


Figure 2. Incidences of long-term all-cause death and cardiac death stratified by D-dimer, hs-CRP, and Lp(a) levels together

(A) Individual D-dimer; (B) Individual hs-CRP; (C) Individual Lp(a); (D) Concurrent D-dimer, hs-CRP, and Lp(a). hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a). ***: $p < 0.001$; *ns.*: non-significant.

However, high D-dimer, high hs-CRP, and high Lp(a) were not associated with the risk of bleeding (Table 2).

Combined cardiovascular risk biomarkers and clinical outcomes

Being categorized by D-dimer, hs-CRP, and Lp(a) levels together, all patients were classified into eight groups. The incidences of all-cause death and cardiac death were highest in high D-dimer-high hs-CRP-high Lp(a) group among the eight groups (Figure 2D). The Kaplan-Meier estimates also showed that high D-dimer-high hs-CRP-high Lp(a) group among eight groups had the highest all--cause death rates (Figure 3D), which were consistent with the results from multivariate Cox analysis in Table 2.

After adjusting for multiple variables, high D-dimer-high hs-CRP-high Lp(a) group had the highest risk of all-cause death and cardiac death among the eight groups, with a 2.714-fold increased risk (HR 2.714, 95% CI: 1.742–4.231) and a 4.152-fold increased risk (HR: 4.152, 95% CI: 2.207–7.812), respectively, compared to low D-dimer-low hs-CRP-low Lp(a) group (which served as the reference group) (Table 2). Additionally, high D-dimer-low hs-CRP-low Lp(a) group, high D-dimer-high hs-CRP-low Lp(a) group, and high D-dimer-low hs-CRP-high Lp(a) group also had a significantly higher risk of all-cause death than low D-dimer-low hs-CRP-low Lp(a) group (with HR values of 1.682, 2.086, and 1.992, respectively, and 95% CI values of 1.082–2.616, 1.355–3.211, and 1.229–3.228, respectively). High D-dimer-low hs-CRP-low Lp(a) group, low D-dimer-low hs-CRP-high Lp(a) group, high D-dimer-high hs-CRP-low Lp(a) group, high D-dimer-low hs-CRP-high Lp(a) group, and low D-dimer-high hs-CRP-high Lp(a) group also had a significantly higher risk of cardiac death than low D-dimer-low hs-CRP-low Lp(a) group (with HR values of 1.951, 2.464, 3.015, 2.996, and 2.632, respectively, and 95% CI values of 1.009–3.776, 1.174–5.173, 1.620–5.615, 1.519–5.909, and 1.166–5.944, respectively) (Table 2).

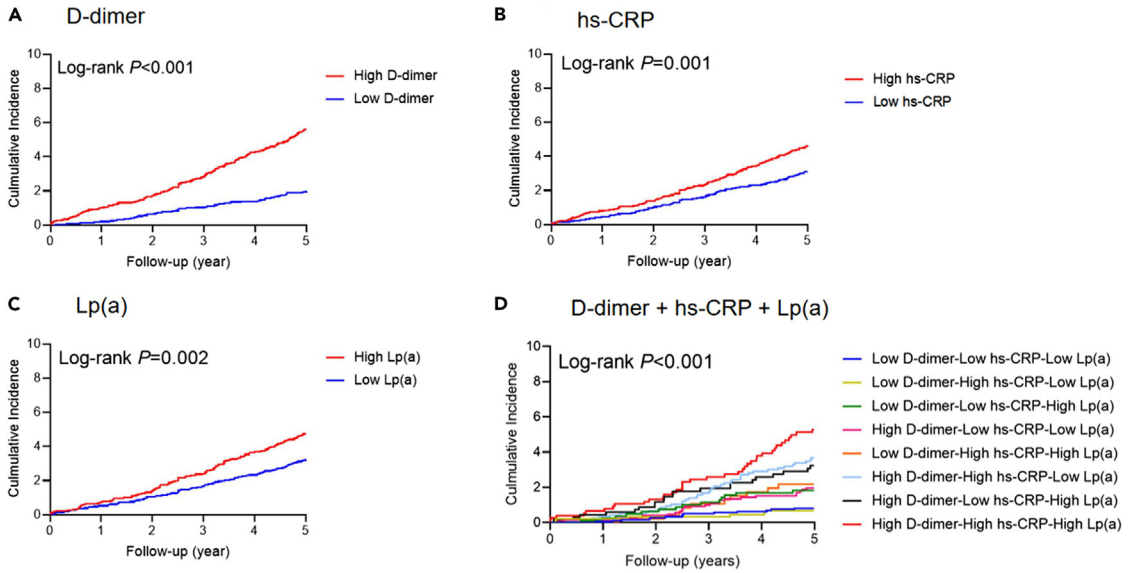


Figure 3. The Kaplan-Meier curves for all-cause death according to cardiovascular risk biomarkers

(A) Individual D-dimer; (B) Individual hs-CRP; (C) Individual Lp(a); (D) Concurrent D-dimer, hs-CRP, and Lp(a). hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a).

However, there was no significant association between these biomarkers in any combined form and bleeding (Table 2).

Incremental value of combined cardiovascular risk biomarkers

The areas under receiver operating characteristic curve (AUCs) (95% CIs) of individually high D-dimer, individually high hs-CRP, and individually high Lp(a) for predicting all-cause death were 0.623 (0.592–0.655), 0.548 (0.514–0.582), and 0.545 (0.511–0.580), respectively; those for predicting cardiac death were 0.628 (0.588–0.668), 0.567 (0.524–0.611), and 0.574 (0.529–0.619), respectively. That of concurrent high D-dimer, high hs-CRP, and high Lp(a) for predicting all-cause death and cardiac death was 0.649 (0.617–0.680) and 0.673 (0.634–0.711), respectively (Figure 4). The addition of a combination of high D-dimer, high hs-CRP, and high Lp(a) to the basic model established with traditional risk factors (age, sex, BMI, smoking, hypertension, diabetes, PAD, COPD, previous myocardial infarction, previous stroke, previous PCI, and previous CABG) significantly improved the discrimination and reclassification for the prediction of all-cause death (C-statistic 0.733 vs. 0.715, $p = 0.008$; net reclassification improvement [NRI] 0.328, $p < 0.001$; integrated discrimination improvement [IDI] 0.007, $p < 0.001$) and cardiac death (C-statistic 0.742 vs. 0.709, $p = 0.002$; NRI 0.511, $p < 0.001$; IDI 0.007, $p < 0.001$) (Table 3).

The AUCs (95% CIs) of individually high D-dimer, individually high hs-CRP, and individually high Lp(a) for predicting bleeding were 0.506 (0.475–0.538), 0.482 (0.451–0.514), and 0.511 (0.479–0.543), respectively. That of concurrent high D-dimer, high hs-CRP, and high Lp(a) for predicting bleeding was 0.524 (0.493–0.555) (Figure 4). When high D-dimer, high hs-CRP, and high Lp(a) were combined with the basic model, there was no significant improvement in discrimination (C-statistic 0.583 vs. 0.588, $p = 0.414$) but there was a significant improvement in reclassification for the prediction of bleeding (NRI 0.154, $p = 0.005$; IDI 0.002, $p = 0.090$) (Table 3).

Subgroup analysis

Although the optimal cutoff values of D-dimer, hs-CRP, and Lp(a) to define high-risk patients in those with ACS and patients with SAP were inconsistent (Table S4), these results were consistent in patients with ACS and patients with SAP (Tables S5 and S6).

Table 2. Multivariate Cox regression of cardiovascular risk biomarkers with clinical outcomes

Cardiovascular risk biomarkers	Category	HR (95% CI) for all-cause death	HR (95% CI) for cardiac death	HR (95% CI) for bleeding
Individual D-dimer				
	Low D-dimer	Ref.	Ref.	Ref.
	High D-dimer	1.922 (1.464–2.522)‡	2.065 (1.443–2.955)‡	0.914 (0.730–1.145)
Individual hs-CRP				
	Low hs-CRP	Ref.	Ref.	Ref.
	High hs-CRP	1.290 (1.014–1.641)*	1.441 (1.051–1.977)*	0.834 (0.665–1.045)
Individual Lp(a)				
	Low Lp(a)	Ref.	Ref.	Ref.
	High Lp(a)	1.409 (1.114–1.783)†	1.796 (1.326–2.434)‡	1.069 (0.855–1.337)
Concurrent D-dimer, hs-CRP, and Lp(a)				
	Low D-dimer-Low hs-CRP-Low Lp(a)	Ref.	Ref.	Ref.
	Low D-dimer-High hs-CRP-Low Lp(a)	0.692 (0.356–1.344)	0.766 (0.293–2.002)	0.767 (0.508–1.160)
	Low D-dimer-Low hs-CRP-High Lp(a)	1.326 (0.746–2.356)	2.464 (1.174–5.173)*	0.882 (0.585–1.329)
	High D-dimer-Low hs-CRP-Low Lp(a)	1.682 (1.082–2.616)*	1.951 (1.009–3.776)*	0.872 (0.616–1.235)
	Low D-dimer-High hs-CRP-High Lp(a)	1.699 (0.921–3.134)	2.632 (1.166–5.944)*	0.969 (0.604–1.555)
	High D-dimer-High hs-CRP-Low Lp(a)	2.086 (1.355–3.211)†	3.015 (1.620–5.615)†	0.713 (0.488–1.040)
	High D-dimer-Low hs-CRP-High Lp(a)	1.992 (1.229–3.228)†	2.996 (1.519–5.909)†	1.020 (0.684–1.522)
	High D-dimer-High hs-CRP-High Lp(a)	2.714 (1.742–4.231)‡	4.152 (2.207–7.812)‡	0.820 (0.540–1.244)

hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); HR, hazard ratio; CI, confidence interval.
The model was adjusted for the following covariates in an all-enter way: age, sex, body mass index, previous PCI, previous CABG, previous myocardial infarction, previous stroke, diabetes, hypertension, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction, and PRECISE-DAPT score.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Sensitivity analysis

In order to assure that Lp(a) was indeed independently associated with the outcomes, we conducted a sensitivity analysis including baseline low-density lipoprotein cholesterol (LDL-C) in multivariable Cox regression. These results were consistent in the sensitivity analysis (Table S7).

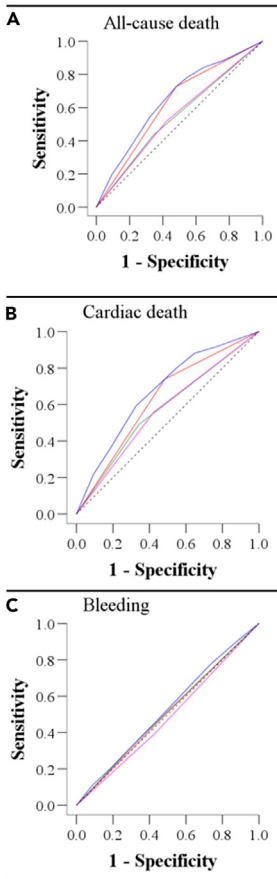
DISCUSSION

This large real-world study of 7,944 participants with a median follow-up of 5.1 years yielded major findings as follows: (a) individually high D-dimer, hs-CRP, and Lp(a) concentrations were associated with higher risks of all-cause death and cardiac death but not with bleeding; (b) patients with concurrent high D-dimer, hs-CRP, and Lp(a) have an augmented adverse effect on all-cause death and cardiac death relative to those with concurrent low D-dimer, hs-CRP, and Lp(a) but not on bleeding; (c) the addition of concurrent high levels of the three cardiovascular risk biomarkers (High D-dimer + High hs-CRP + High Lp(a)) to the basic model established with traditional risk factors (age, sex, BMI, smoking, hypertension, diabetes, PAD, COPD, previous myocardial infarction, previous stroke, previous PCI, and previous CABG) resulted in an incremental effect on the predictive value for all-cause and cardiac death.

The synergistic effect of cardiovascular risk biomarkers on prognosis

Despite promising results in recent pharmaceutical investigations aimed at lowering the risk of cardiovascular recurrent events in the secondary prevention population,[18] the exact mechanisms remain unclear and more effective instruments are needed for accurate risk quantification.[19] As a result, it is necessary to identify more appropriate contributors to further identify high-risk patients and reduce cardiovascular risk.

D-dimer, hs-CRP, and Lp(a) are well-established cardiovascular risk factors that can mediate the risk of cardiovascular recurrent events. Recent studies have supported D-dimer as a biomarker of thrombotic



All-cause death	AUC (95% CI)	P Value	PPV	NPV
High D-dimer	0.623 (0.592–0.655)	<0.001	0.053	0.981
High hs-CRP	0.548 (0.514–0.582)	0.006	0.044	0.970
High Lp(a)	0.545 (0.511–0.580)	0.009	0.045	0.969
High D-dimer + High hs-CRP + High Lp(a)	0.649 (0.617–0.680)	<0.001	0.053	0.981

Cardiac death	AUC (95% CI)	P Value	PPV	NPV
High D-dimer	0.628 (0.588–0.668)	<0.001	0.032	0.989
High hs-CRP	0.567 (0.524–0.611)	0.003	0.028	0.984
High Lp(a)	0.574 (0.529–0.619)	0.001	0.030	0.983
High D-dimer + High hs-CRP + High Lp(a)	0.673 (0.634–0.711)	<0.001	0.038	0.987

Bleeding	AUC (95% CI)	P Value	PPV	NPV
High D-dimer	0.506 (0.475–0.538)	0.702	0.043	0.959
High hs-CRP	0.482 (0.451–0.514)	0.277	–	0.958
High Lp(a)	0.511 (0.479–0.543)	0.499	0.045	0.959
High D-dimer + High hs-CRP + High Lp(a)	0.524 (0.493–0.555)	0.141	0.044	0.964

Figure 4. Predictive value for clinical outcomes according to cardiovascular risk biomarkers

(A) All-cause death; (B) Cardiac death; (C) Bleeding. AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a).

risk.[6,12,17] A meta-analysis showed that D-dimer was associated with higher in-hospital and short/long-term complications in patients with ACS.[6] The long-term intervention with pravastatin in ischaemic disease (LIPID) study demonstrated that D-dimer was an independent risk factor for predicting long-term risk of cardiac death, and this association persisted after a ten-year follow-up.[17] In our previous studies, D-dimer was independently associated with long-term risk of all-cause and cardiac death in patients with PCI.[12] In terms of the biomarker of inflammatory risk, hs-CRP is a common and effective biomarker to determine the level of inflammation. Anti-inflammatory therapy has been proven to improve the prognosis in patients with CHD with elevated hs-CRP levels.[4,7] Regarding Lp(a), it is a well-known independent risk factor of atherosclerotic cardiovascular disease, and the increased cardiovascular risk associated with elevated Lp(a) on a per-particle basis may exceed that of LDL-C.[20] Large-scale studies have shown that elevated Lp(a) levels remained a major risk factor for adverse outcomes in statin-treated patients with low LDL-C.[8,21,22]

Of interest, according to the most current studies, when the presence of more than one risk factor is identified, as is common, their effects on the risk of recurrence of adverse events may be synergistic.[23] Liu et al. demonstrated that patients with high levels of three cardiovascular risk factors concurrently (remnant cholesterol, Lp(a), hs-CRP) had a worse outcome than those with low levels concomitantly, indicating a synergistic relationship of cardiovascular risk factors for predicting major adverse cardiovascular events in patients with chronic coronary syndrome.[15] Therefore, the evaluation and management of combined risk factors play an important role in the risk stratification of atherosclerotic cardiovascular disease. In the present study, we classified the population into eight groups according to D-dimer, hs-CRP, and Lp(a) levels together and found that the concurrent high levels of the three cardiovascular risk factors (High

Table 3. Additional prognostic information provided by cardiovascular risk biomarkers beyond the basic model of traditional risk factors

	C-statistic (95% CI)	p value	NRI (95% CI)	p value	IDI (95% CI)	p value
All-cause death						
Basic model[a]	0.715 (0.684–0.746)	Ref.	–	Ref.	–	Ref.
Basic model + High D-dimer + High hs-CRP + High Lp(a)	0.733 (0.703–0.763)	0.008	0.328 (0.213–0.443)	<0.001	0.007 (0.005–0.010)	<0.001
Cardiac death						
Basic model[a]	0.709 (0.668–0.751)	Ref.	–	Ref.	–	Ref.
Basic model + High D-dimer + High hs-CRP + High Lp(a)	0.742 (0.703–0.781)	0.002	0.511 (0.367–0.655)	<0.001	0.007 (0.004–0.011)	<0.001
Bleeding						
Basic model[a]	0.583 (0.552–0.615)	Ref.	–	Ref.	–	Ref.
Basic model + High D-dimer + High hs-CRP + High Lp(a)	0.588 (0.557–0.618)	0.414	0.154 (0.046–0.262)	0.005	<0.001 (<0.001–<0.001)	0.090

hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

[a]Covariates included in the model were age, sex, BMI, smoking, hypertension, diabetes, PAD, COPD, previous myocardial infarction, previous stroke, previous PCI, and previous CABG.

D-dimer-High hs-CRP-High Lp(a)) significantly deteriorated the 5-year all-cause and cardiac death (with the highest HR among all groups) although there was no such effect on the 5-year bleeding. In short, this study established that there was a synergistic relationship between D-dimer, hs-CRP, and Lp(a) for predicting the ischemic prognosis in PCI patients. It is known that elevated concentrations of these cardiovascular risk biomarkers are associated with many pathological processes; however, the mechanism of how D-dimer, hs-CRP, and Lp(a) predict mortality remains unclear. Previous studies showed that elevated D-dimer was related to thrombosis,[24] plaque necrosis,[24] and infection,[25] whereas elevated hs-CRP was related to high platelet reactivity,[26] smooth muscle cell proliferation, human macrophage polarization,[27] and thromboxane activity.[27] Furthermore, elevated Lp(a) was related to endothelial damage,[28] inflammatory response,[29] and fibrinolytic inhibition.[30] These reasons may explain why D-dimer, hs-CRP, and Lp(a) were independent risk biomarkers for all-cause death and cardiac death.

The incremental value beyond the basic model of established risk factors

A recent investigation has demonstrated that a multi-biomarker score outperforms a single biomarker in terms of predictive value.[31] Prior studies have indicated that the addition of individual D-dimer, individual hs-CRP, and individual Lp (a) to the model of established risk factors can improve the predictive value for ischemic events.[32–34] In light of our findings, there was a synergistic effect of D-dimer, hs-CRP, and Lp(a) on prognosis. To our best knowledge, there have been no studies focusing on the combined effects of these three biomarkers. Accordingly, this was the inaugural study to simultaneously focus on the role of these three biomarkers in the risk of adverse events in a CHD secondary prevention population. By adding elevated D-dimer, hs-CRP, and Lp(a) as a combination to the basic model of established risk factors, we observed that the new model exhibited a significant improvement in predictive value for long-term all-cause death and cardiac death.

In our study, all subjects enrolled were secondary prevention patients with CHD who had undergone PCI treatment. On the basis of traditional risk factor control, the majority of patients (96.1%) received statins while traditional antihypertensive therapy and hypoglycemic therapy were administrated as appropriate. But even so, the risk of adverse events persisted, highlighting the importance of identifying high-risk patients. Embarking on thrombosis, inflammation, and lipid risk, we concurrently focused on three commonly used clinical laboratory biomarkers, namely D-dimer, hs-CRP, and Lp(a) levels, and found that patients with simultaneously elevated levels of all three had a 3- to 4-fold higher risk of recurrent adverse events. Our findings had important guiding implications for clinical practice as simultaneously monitoring these three biomarkers may aid in identifying high-risk patients and initiating intensive treatment to improve their prognosis.

In conclusion, this large-sample, real-world study showed that each individual elevation of D-dimer, hs-CRP, and Lp(a) was associated with poor ischemic outcomes. Furthermore, the concurrent elevation of D-dimer, hs-CRP, and Lp(a) was related to an even greater risk of poor ischemic prognosis and improved prognostic accuracy of the traditional risk factors model. Our findings may shed light on the potential utility of combining these cardiovascular risk biomarkers to enhance risk stratification in the PCI population.

Limitations of the study

Our study had several limitations. First, this was a single-center, observational study. Therefore, this study has the inherent defects of an observational study. Second, although we attempted to adjust as many important confounding factors as possible, the study could still suffer from residual confounding. Third, our study population was enrolled in 2013 when ticagrelor was first introduced to China, so the vast majority of patients (99.8%) in this study were on clopidogrel. In the future, further research on patients treated with ticagrelor needs to be carried out.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107030.

ACKNOWLEDGMENTS

Thanks for the data collection, analysis, revision, and monitoring by all contributors in this study.

Sources of funding: This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2020-I2M-C&T-B-052); the National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (grant number NCRC2020013); Young and middle-aged talents in the XPCC Science and Technology Project (grant number 2020CB012); CS Optimizing Antithrombotic Research Fund (grant number BJUHFCSOARF201801-06).

AUTHOR CONTRIBUTIONS

LJW and ZXY contributed to the concept and design of the study; LJW wrote the manuscript; LJW conducted the statistical analysis; ZXY and YJQ revised the intellectual content; LJW, ZP, TXF, JL, LYL, and YKL contributed to data collection; YWX, QSB, XB, YYJ, and GRL contributed to interpretation of data; all authors approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

Received: April 5, 2023
Revised: May 1, 2023
Accepted: May 31, 2023
Published: June 7, 2023

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical commercial assays		
D-dimer	Stago-R Evolution (France) automatic coagulation analyzer	N/A
hs-CRP	An automated biochemical analyzer (LABOSPECT 008, HITACHI, Japan)	N/A
Lp(a)	A latex turbidimetric method [LASAY Lp(a) auto; SHIMA laboratories; Tokyo, Japan]	N/A
Software and algorithms		
SPSS Statistics Version 23.0	IBM, Chicago, IL, USA	https://www.ibm.com/products/spss-statistics
R Programming Language version 4.0.3	Foundation for Statistical Computing, Vienna, Austria	https://www.r-project.org

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xueyan Zhao (zhao_xueyan@sina.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The complete original data reported in this study cannot be deposited in a public repository because these data are confidential medical records. To request access, contact Dr. Xueyan Zhao (zhao_xueyan@sina.com).
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design and participants

The present study was based on a real-world, prospective, single-centre, and observational cohort. From January 2013 to December 2013, 10,724 patients who were treated with PCI were consecutively and prospectively enrolled in Fu Wai Hospital (Beijing, China). All participants in this study were Chinese patients [n = 7,944; males = 6,067 (76.4%); mean age = 58.4 years]. We excluded patients who (a) were receiving oral anticoagulant therapy, (b) underwent balloon dilatation without stent implantation, (c) had missing D-dimer, hs-CRP, and Lp(a) data, and (d) were lost to follow-up. Finally, a total of 7,944 eligible patients were enrolled for analysis. After PCI, dual-antiplatelet therapy consisting of aspirin 100 mg daily and clopidogrel 75 mg daily or ticagrelor 90 mg twice daily was administered for at least 12 months in all participants. This study complied with the Helsinki Declaration. The Review Board of Fu Wai Hospital approved the study protocol (Approval Number: 2013-449). All participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

METHOD DETAILS

Blood sampling and biomarker measurement

Blood samples were collected by direct venipuncture within 24 hours after admission, using EDTA-anticoagulant tubes. The samples were centrifuged to produce plasma. Plasma D-dimer concentrations were

measured using a Stago-R Evolution (France) automatic coagulation analyzer. Plasma hs-CRP concentrations were measured using an automated biochemical analyzer (LABOSPECT 008, HITACHI, Japan). Plasma Lp(a) concentrations were measured using an immunoturbidimetry method according to the manufacturer's guide, a latex turbidimetric method [LASAY Lp(a) auto; SHIMA laboratories; Tokyo, Japan].

Clinical outcomes and follow-up

The primary endpoint was all-cause death. The secondary endpoints were cardiac death and bleeding. According to the Bleeding Academic Research Consortium (BARC), the definition of bleeding was BARC type 2, 3, or 5 bleeding. Follow-ups were regularly conducted through clinic visits or by telephone interviews at 30 days, 6 months, 1 year, 2 years, and 5 years, with a 91.54% follow-up rate at 5 years. All endpoint events were adjudicated centrally by two independent cardiologists, and possible disagreement was resolved by consensus.

QUANTIFICATION AND STATISTICAL ANALYSIS

Participants were stratified into two groups according to the cut-off point of D-dimer levels. We also conducted stratification for individual hs-CRP and Lp(a). In accordance with previously published studies, the cut-off points of D-dimer, hs-CRP, and Lp(a) levels in this study were 0.28 μg/mL FEU (fibrinogen-equivalent unit)[12] (also the median of D-dimer concentrations in our study), 2 mg/L,[35] 30 mg/dL,[13] respectively. These points were more clinically meaningful and convenient in clinical practice, which were close to the value of optimal cut-off points we calculated by Youden's index (Table S4).

Continuous variables were reported as means ± standard deviation (SD) or medians (interquartile range, IQR) and were compared by Student's *t*-test or nonparametric test. Categorical variables were expressed as frequency (%) and compared by χ^2 or Fisher exact test.

The risk of primary endpoint among different groups were compared by log-rank test and presented by Kaplan-Meier survival curves. The independent associations between individual and combined cardiovascular risk biomarkers and long-term clinical outcomes were studied using multivariable Cox proportional hazard regressions to calculate the hazard ratio (HR) and 95% confidence interval (CI). To evaluate the non-linear association of cardiovascular risk biomarkers with long-term clinical outcomes, the analyses were performed by using a multivariate Cox model with a restricted cubic spline. The multivariate model was adjusted for the following covariates in an all-enter way: age, sex, body mass index, previous PCI, previous coronary artery bypass grafting, previous myocardial infarction, previous stroke, diabetes, hypertension, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction, and PRECISE-DAPT score.

The predictive value of single and combined cardiovascular risk biomarkers on clinical outcomes was assessed by area under the receiver operating characteristic curve (AUC). To assess the incremental value of combined cardiovascular risk biomarkers beyond a basic model established with traditional risk factors, the C-statistic, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated.

Subgroup analyses for patients with ACS and patients with SAP were conducted. Given different types of patients may have different optimal cut-off points, receiver operating characteristic curve (ROC) analysis was performed to get the Youden's indexes for patients with ACS and patients with SAP; the Youden's index with the greatest sensitivity and specificity was used to determine the optimal cut-off values for D-dimer, hs-CRP, and Lp(a) to predict long-term all-cause death. All of the subgroup analyses were based on these calculated optimal cut-off points (Table S4).

All statistical analyses were performed at a significance level of two-sided 0.05. Statistical analyses were performed via SPSS version 23.0 (IBM, Chicago, IL, USA), and R Programming Language version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).