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ORIGINAL RESEARCH

Comparative Evaluation of Prolonged Dual Antiplatelet Therapy versus Conventional Regimens on Prognosis in Patients with High Residual Inflammatory Risk: Results from a Prospective Observational Study

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Introduction: High residual inflammatory risk (hs-CRP≥2mg/L) predicts worse prognosis and increased ischemic risk following percutaneous coronary intervention (PCI). The optimal duration of dual antiplatelet therapy (DAPT) and its risk-benefit profile in post-PCI patients with high residual inflammatory risk remain unclear.

Methods: Patients undergoing PCI with high residual inflammatory risk at Fuwai Hospital were consecutively enrolled. Patients were stratified into two groups based on DAPT duration: prolonged (>12 months) and conventional (≤12 months) groups. The primary outcome was a composite endpoint of all-cause death, myocardial infarction, definite or probable stent thrombosis, or stroke at 3 years. The key safety outcome was the 3-year rate of Bleeding Academic Research Consortium 2, 3, or 5 bleeding.

Results: Among post-PCI patients with high residual inflammatory risk, 2440 individuals (69.5%) continued DAPT beyond 12 months. After three years of follow-up, prolonged DAPT was associated with a significantly lower risk of the primary outcome (1.5% vs. 4.2%; adjusted hazard ratio [HR]: 0.347, 95% CI: 0.224–0.539). Similar benefits were observed for net adverse clinical events (1.4% vs. 4.1%; adjusted HR: 0.338, 95% CI: 0.216–0.53) and for the composite endpoint of all-cause death or myocardial infarction (0.6% vs. 3.1%; adjusted HR: 0.182, 95% CI: 0.097–0.341). Notably, the key safety endpoint did not differ significantly between the two DAPT durations during follow-up (1.0% vs. 1.2%; adjusted HR: 0.793, 95% CI: 0.401–1.57).

Conclusion: In patients who underwent PCI with high residual inflammatory risk, prolonged DAPT improved clinical outcomes by mitigating ischemic risk without increasing clinically significant bleeding.

Keywords: blood platelets, inflammation, percutaneous coronary intervention, high-sensitivity C-reactive protein

Introduction

Despite the widespread use of more effective lipid-lowering therapies, inflammation remains a prominent driver of residual cardiovascular risk.[1,2] Inflammation, as assessed by high-sensitivity C-reactive protein (hs-CRP), has been recognized as a more potent predictor of future cardiovascular events and mortality than low-density lipoprotein cholesterol (LDL-C).[3] Patients who underwent percutaneous coronary intervention (PCI) with residual inflammatory risk (hs-CRP ≥ 2 mg/L)

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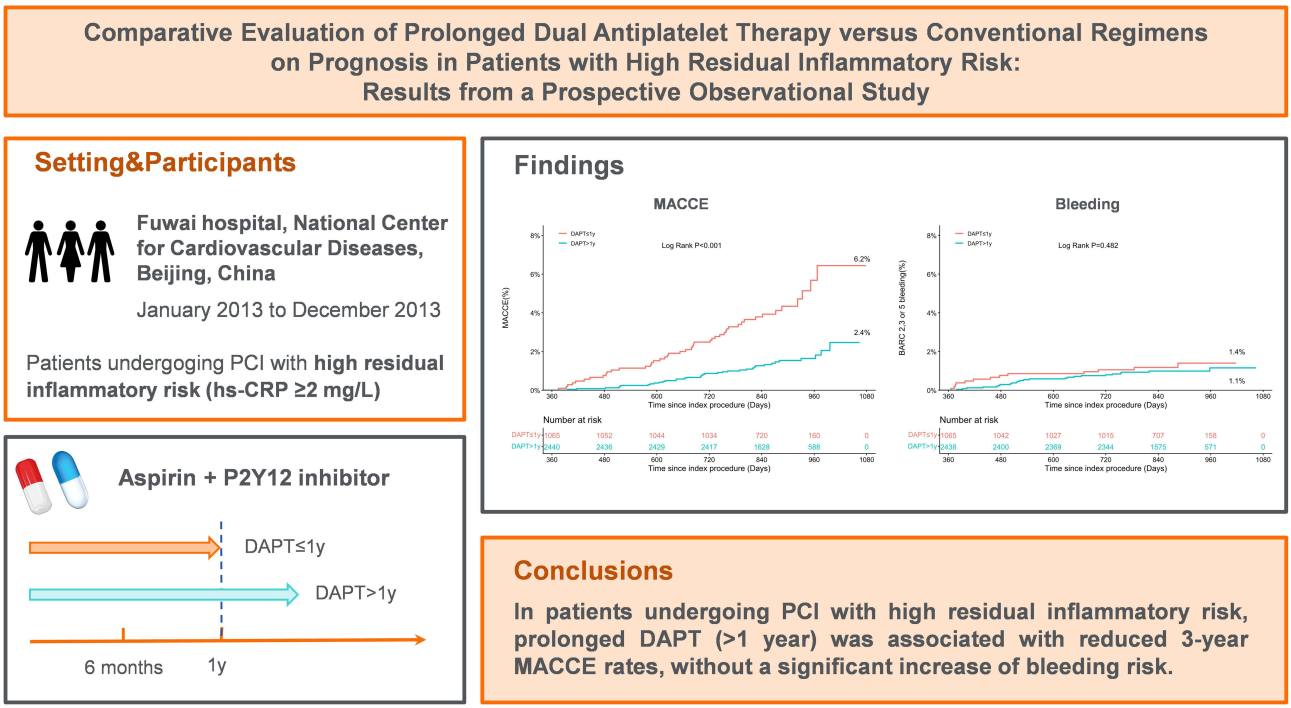
Graphical Abstract



experienced significantly higher rates of all-cause mortality, major adverse cardiovascular events, and myocardial infarction (MI),[2,4,5] indicating a possible need for more intensive secondary prevention strategies for those patients.

Dual antiplatelet therapy, consisting of aspirin and a $P2Y_{12}$ inhibitor, is the standard of care for preventing atherothrombotic events in patients undergoing PCI with either acute or chronic coronary syndrome.[6,7] However, the optimal duration of DAPT following PCI remains a topic of ongoing debate.[8,9] Several DAPT modulation strategies have been developed to improve outcomes in a precision medicine approach.[10,11] Therefore, determining the optimal duration of DAPT remains a clinical challenge, which requires a delicate balance between ischemic and bleeding risks informed by individual patient characteristics and clinical circumstances.[12]

The current guideline-recommended DAPT duration is based mainly on the balance between ischemic and bleeding risks in the general post-PCI population,[6,7,13,14] and DAPT of 12 months is generally recommended for acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) with high ischemic risk.[6,7] High residual inflammatory risk (≥2 mg/L) was present in 40~50% of patients undergoing PCI,[4,15] and these patients had a significantly higher ischemic risk than those with lower hs-CRP levels.[16,17] In addition, inflammation is involved in the platelet and coagulation cascade activation, suggesting the potential benefit of intensive antiplatelet therapy in patients with high residual inflammatory risk.[18] So far, however, no specific recommendations have been issued by existing guidelines for this subgroup of patients. Evidence evaluating the benefit-risk trade-off of different DAPT durations in these patients is scarce, leaving a critical knowledge gap. Therefore, we aimed to investigate the effectiveness and risks of DAPT beyond 12 months versus the conventional regimen (≤12 months) in post-PCI patients with high residual inflammatory risk, and to explore whether the effect of DAPT duration is influenced by the degree of inflammatory elevation, using data from a large, prospective PCI registry.

Materials and Methods

Study Design and Population

This was an analysis using data from the Fuwai Percutaneous Coronary Intervention Registry, which consecutively enrolled patients with coronary artery disease undergoing PCI with drug-eluting stent (DES) implantation from January 2013 to December 2013 at Fuwai Hospital, National Center for Cardiovascular Diseases (Beijing, China). The details of the study design were previously reported.[19,20] Clinical indications for PCI included: significant stenosis (non-left main >70% and/or left main >50%) with typical myocardial ischemia symptoms, and severe stenosis (non-left main ≥90%) with atypical symptoms of myocardial ischemia. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Fuwai Hospital (Approval Number 2016–847). All eligible patients provided written informed consent before enrollment. This study adhered to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines.

Patients with high residual inflammatory risk, defined as a preoperative high-sensitivity C-reactive protein (hs-CRP) level of 2 mg/L or higher,[4,21] were enrolled in this study. This threshold is recommended by the 2025 ACC Scientific Statement for identifying residual inflammatory risk,[22] and it predicts recurrent ischemic events and worse clinical outcomes in the secondary prevention setting.[3,23] In East Asian populations, patients undergoing PCI with hs-CRP ≥2 mg/L had a higher risk of ischemic events and cardiovascular death.[16,17,24] Hence, the ≥2 mg/L cutoff is a well-validated and clinically relevant threshold for post-PCI secondary prevention risk stratification.

Participants were excluded if their data on antiplatelet therapy were missing or if they experienced adverse events (death, myocardial infarction, stroke, repeated revascularization, stent thrombosis, or Bleeding Academic Research Consortium [BARC] type 2, 3, or 5 bleeding) within 12 months after initial PCI. The detailed flow chart is presented in Figure 1.

Procedures and Biochemical Analysis

All PCI procedures and medical therapy during hospitalization were conducted according to the guidelines and at the discretion of cardiologists, as previously described.[25]

Unfractionated heparin or bivalirudin was used for anticoagulation during the procedure. Coronary angiographic and procedural data were interpreted and documented by two independent interventional cardiologists from catheter laboratory records.

Prior to the coronary intervention, blood samples were collected following at least 12-hour fasting for biochemical analysis. All tests were conducted in the clinical chemistry department of Fuwai Hospital. The level of hs-CRP was examined with standard biochemical techniques at the core laboratory of Fuwai Hospital. Concentrations of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, fasting plasma glucose (FPG), and creatinine were examined using the same methods as reported before.[26]

DAPT and Data Collection

Before PCI, all patients received loading doses of aspirin (300 mg) and a $P2Y_{12}$ inhibitor (clopidogrel 300 or 600 mg), unless they had already been prescribed these antiplatelet medications. After coronary intervention, aspirin 100 mg/day was prescribed indefinitely, and clopidogrel 75 mg/day was typically administered for 12 months unless there were undisputed reasons to stop DAPT. Whether to discontinue or continue the DAPT after 1 year was determined mainly by the patients' treating physicians based on individual ischemic and bleeding risks, and the patients' preferences.

Demographic and clinical data of all participants were collected by independent research personnel. Demographic data were comprised of age, gender, body mass index (BMI), concomitant diseases, smoking status, previous myocardial infarction, and revascularization history (PCI or coronary artery bypass grafting [CABG]). Clinical information included the initial diagnosis at admission, results from physical examinations, medical imaging, laboratory tests, and medications prescribed at discharge.

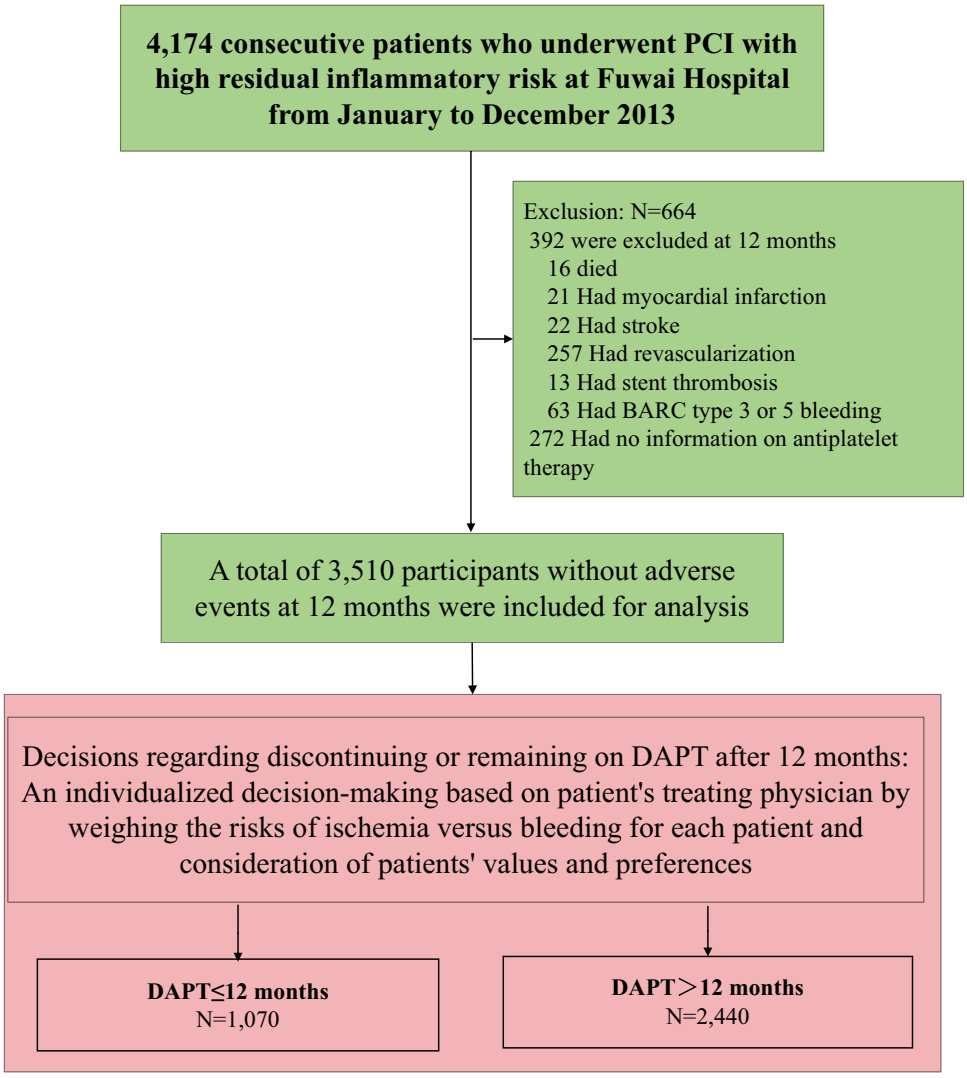


Figure 1 Flowchart of the study population.
Abbreviations: DAPT, dual antiplatelet therapy; High residual inflammatory risk was defined as having a preoperative high-sensitivity C-reactive protein (hs-CRP) level of 2 or higher.

Follow-Up and Study Endpoints

After the index PCI, patients were followed up at 1, 6, and 12 months and then annually. Follow-up data were collected via medical records, clinical visits, or telephone interviews by well-trained investigators who were blinded to the study design and patients' clinical information, through the end of the follow-up period or until death. At each follow-up visit, information on patients' clinical status, angiographic and procedural characteristics, and adverse events (including but not limited to death, MI, stroke, definite or probable stent thrombosis, bleeding, repeat revascularization procedures, repeat hospitalization for any reason, and results of such, if applicable) was documented. Specifically, adherence to antiplatelet medication was routinely assessed by recording the exact start date (first dose taken) and exact stop date (last dose taken), including identifying the decision maker (ie, who decided the start or stop) and the reason each antiplatelet medication was stopped. Patients were advised to return for coronary angiography if any indications of ischemic events emerged. To obtain follow-up information for more than 2 years per patient, the follow-up period was extended to January 31, 2016. The status of antiplatelet therapy was acquired by dedicated questionnaires and the electronic prescribing system at Fuwai Hospital.

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), which was defined as a composite of all-cause mortality, MI, stroke (hemorrhagic or ischemic), or definite or probable stent thrombosis at 3 years after the index PCI. The key safety outcome was BARC type 2, 3, or 5 bleeding. The major secondary endpoint was net adverse clinical events (NACE), a composite of cardiac death, target-vessel MI, clinically driven target-lesion revascularization, stent thrombosis, or major bleeding (BARC type 3 or 5). Other secondary endpoints included death from any cause or MI, death from cardiovascular causes, death from any cause, MI, target vessel revascularization, definite or probable stent thrombosis, and stroke.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and were compared using 2-sample Student's t-tests or the Mann–Whitney *U*-test as appropriate. Categorical variables were presented as counts and percentages and were compared using the chi-square test or Fisher's exact test as appropriate. The cumulative incidence of clinical events was estimated using Kaplan-Meier curves, and the differences were compared using the Log rank test. Univariable and multivariable Cox regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Variables significantly associated with the outcomes in the univariate Cox regression analysis ($P < 0.05$, Supplementary Table 1), or considered clinically relevant, were included in the multivariable Cox regression models. The following covariates were included in the final multivariable model: age, sex, BMI, diabetes, dyslipidemia, hypertension, chronic kidney disease (CKD), previous MI, and left ventricular ejection fraction (LVEF). Subgroup analyses were conducted to investigate the relationships between differences in the DAPT duration and MACCEs in patients stratified by age (< 75 vs. ≥ 75 years), sex (male vs. female), diabetes status (yes vs. no), hypertension (yes vs. no), dyslipidemia (yes vs. no), CKD (yes vs. no), history of MI (yes vs. no), current smoker (yes vs. no), or clinical presentation (ACS vs. CCS). In the subgroup analyses, all covariates used in the primary multivariable Cox regression were retained, excluding the variable used to define the subgroups. To evaluate effect modification, we performed a likelihood ratio test comparing the original regression model with the model that included an interaction term between the subgroup indicator and DAPT duration; the resulting *P* value was reported as the *P* for interaction. The interaction between hs-CRP tertiles and DAPT duration was also explored. A two-sided $P < 0.05$ was considered to indicate statistical significance unless otherwise specified. All statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Among 10724 patients undergoing PCI (January to December 2013, Fuwai PCI registry), 4174 patients presented with high residual inflammatory risk (preoperative hs-CRP ≥2 mg/L). A total of 3510 patients were included after excluding 272 without antiplatelet information and 392 with adverse events within 12 months after PCI (Figure 1). The mean age of enrolled patients was 58.36 ± 10.36 years, and 76.5% (2684/3510) were male (Table 1). The median hs-CRP in the overall population was 4.24 (2.75, 9.04) mg/L.

The enrolled population comprised 1070 patients receiving DAPT for ≤1 year and 2440 patients receiving DAPT for >1 year. Patients taking DAPT for ≤1 year had a higher proportion of acute MI (27.4% vs 23.7%, *P*=0.024), and were less likely to have left main or multivessel coronary artery disease (74.0% vs 79.6%, *P*<0.001). There was no significant difference in the median hs-CRP levels between the two groups. The mean duration of DAPT for the whole group was 571.35 ± 203.94 days, with a mean duration of 351.10 ± 50.09 days for the conventional DAPT group and 667.93 ± 167.70 days for the prolonged DAPT group (Table 2).

Clinical Outcomes

After the 3-year follow-up, a total of 82 MACCEs and 37 BARC 2, 3, or 5 bleeding events were recorded. The clinical outcomes stratified by DAPT duration are presented in Figure 2 and Table 3. In the multivariable Cox regression analysis, prolonged DAPT was associated with a significantly lower prevalence of 3-year MACCEs (adjusted HR=0.347, 95% CI:

Table 1 Baseline Characteristics of Patients with High Residual Inflammatory Risk Undergoing PCI: a Comparison of DAPT Duration >12 Months vs ≤12 Months

	Total (N=3,510)	DAPT ≤12 Months (N =1,070)	DAPT >12 Months (N =2,440)	*P* value
Age, yrs	58.36±10.36	58.63±10.38	58.24±10.35	0.311
Age >75y (%)	226(6.4)	76(7.1)	150(6.1)	0.324
Male, n (%)	2684(76.5)	817(76.4)	1867(76.5)	0.952
BMI, kg/m^2	26.35±3.25	26.30±3.39	26.36±3.19	0.595
Hypertension, n (%)	2352(67.0)	704(65.8)	1648(67.5)	0.33
Diabetes, n (%)	1129(32.2)	344(32.1)	785(32.2)	1
dyslipidemia, n (%)	2366(67.4)	698(65.2)	1668(68.4)	0.075
Smoking, n (%)	2081(59.3)	644(60.2)	1437(58.9)	0.496
Previous PCI, n (%)	669(19.1)	196(18.3)	473(19.4)	0.487
Previous Cerebrovascular diseases, n (%)	390(11.1)	108(10.1)	282(11.6)	0.225
Peripheral vascular disease, n (%)	86(2.5)	23(2.1)	63(2.6)	0.519
COPD, n (%)	106(3.0)	29(2.7)	77(3.2)	0.547
Acute myocardial infarction, n (%)	872(24.8)	293(27.4)	579(23.7)	0.024
Acute coronary syndrome, n (%)	2335(66.5)	729(68.1)	1606(65.8)	0.195
Left ventricular ejection fraction, %	62.45(7.39)	62.31(7.60)	62.52(7.29)	0.449
SS	11.84(8.12)	11.74(8.22)	11.88(8.07)	0.624
Left main artery/multi-vessels	2734(77.9)	792(74.0)	1942(79.6)	<0.001
Clinical presentation				
Silent ischemia	216(6.2)	62(5.8)	154(6.3)	0.61
Stable angina	959(27.3)	279(26.1)	680(27.9)	0.291
Unstable angina	1463(41.7)	436(40.7)	1027(42.1)	0.481
NSTEMI	249(7.1)	77(7.2)	172(7.0)	0.932
STEMI	623(17.7)	216(20.2)	407(16.7)	0.014
Laboratory tests				
eGFR, $mL/min/1.73m^2$	95.50±16.84	95.16±16.92	95.65±16.81	0.43
Hemoglobin, g/dL	142.22±15.57	141.81±15.71	142.40±15.50	0.297
Platelet count, $10^9/L$	218.02±59.83	221.39±59.52	216.55±59.91	0.027
White blood cell, $10^9/L$	7.15±1.66	7.21±1.68	7.12±1.64	0.136
Serum creatinine, mg/dL	76.42±16.93	76.46±16.58	76.40±17.09	0.923
Hs-CRP, mg/L	4.24 (2.75, 9.04)	4.24 (2.75, 9.04)	4.23 (2.75, 9.04)	0.991
TC, mmol/L	4.35±1.08	4.33±1.05	4.36±1.10	0.493
LDL, mmol/L	2.63±0.91	2.61±0.88	2.64±0.93	0.452
HDL, mmol/L	0.99±0.26	0.99±0.26	0.98±0.26	0.17
Lpa, nmol/L	20.84 (9.08, 43.81)	20.84 (9.08, 43.81)	20.83 (9.08, 43.81)	0.993
HbA1C, %	6.75±1.29	6.68±1.25	6.78±1.31	0.04

Abbreviations: DAPT, dual antiplatelet therapy; BMI, body mass index; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SS, SYNTAX Score, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-segment-elevation myocardial infarction; hs-CRP, high-sensitivity C-reactive protein.

Table 2 Medication Information of Patients with High Residual Inflammatory Risk Undergoing PCI: a Comparison of DAPT Duration >12 Months Vs ≤12 Months

	Total (N=3,510)	DAPT ≤12 Months (N =1,070)	DAPT >12 Months (N =2,440)	*P* value
Medication at discharge				
Taking aspirin	3510(100)	1070(100)	2440(100.0)	1
Taking clopidogrel	3510(100)	1070(100)	2440(100.0)	1
Taking DAPT	3510(100)	1070(100)	2440(100.0)	1

(*Continued*)

Table 2 (Continued).

	Total (N=3,510)	DAPT ≤12 Months (N =1,070)	DAPT >12 Months (N =2,440)	*P* value
DAPT Score	2.10 (1.15)	2.09 (1.18)	2.10 (1.13)	0.907
DAPT Score≥2	2496(71.1)	750(70.1)	1746(71.6)	0.401
Nitrates	3440(98.0)	1049(98.0)	2391(98.0)	1
Fondaparinux	1101(31.4)	344(32.1)	757(31.0)	0.534
Chronic oral anticoagulant	9(0.3)	3(0.3)	6(0.2)	1
Calcium channel blockers	1710(48.7)	514(48.0)	1196(49.0)	0.619
β-blockers	3200(91.2)	982(91.8)	2218(90.9)	0.438
Statin	3368(96.0)	1023(95.6)	2345(96.1)	0.055
Calcium channel blockers	669(19.1)	196(18.3)	473(19.4)	0.487
At 12-mo visit				
Taking aspirin	3421(97.5)	981(91.7)	2440(100.0)	<0.001
Taking clopidogrel	2460(70.1)	20(1.9)	2440(100.0)	<0.001
Taking DAPT	2440(69.5)	0(0.0)	2440(100.0)	<0.001
At 24-mo visit				
Taking aspirin	3320(94.6)	969(90.6)	2351(96.4)	<0.001
Taking clopidogrel	878(25.0)	16(1.5)	862(35.3)	<0.001
Taking DAPT	829(23.6)	0(0.0)	829(34.0)	<0.001
Duration of DAPT	571.35±203.94	351.10±50.09	667.93±167.70	<0.001

Abbreviation: DAPT, dual antiplatelet therapy.

0.224–0.539, Table 4) compared with DAPT ≤1 year. The adjusted HR for the key safety outcome was 0.793 (95% CI: 0.401–1.57) for patients taking DAPT>1 year versus DAPT≤1 year.

The 3-year NACE risk was significantly lower in the prolonged DAPT group (adjusted HR=0.338, 95% CI: 0.216–0.53, Table 3). A similar trend was observed for the composite endpoint of death from any cause or MI among patients taking DAPT for >1 year (adjusted HR=0.182, 95% CI: 0.097–0.341). Additionally, patients with prolonged DAPT also had lower rates of death from cardiovascular causes (0 vs. 1.8%), death from any cause (0 vs. 3.0%), and definite or probable stent thrombosis (0.2% vs. 1.4%) at 3-year follow-up (all *P* values <0.001). Intriguingly, the 3-year cumulative incidence of target vessel revascularization was higher in the prolonged DAPT group (2.1% vs. 0.9%, p=0.019).

Subgroup Analysis According to DAPT Duration

The reduced MACCEs associated with prolonged DAPT remained consistent across subgroups defined by age (<75 vs. ≥ 75 years), sex, hypertension, dyslipidemia, CKD, history of MI, current smoker, and clinical presentation (ACS vs. CCS) (all *P* for interaction values >0.05, Table 5). Diabetes was identified as an effect modifier of the relationship between DAPT duration and 3-year MACCE risk (*P* for interaction=0.025). Importantly, however, prolonged DAPT (>1 year) was associated with a lower cumulative incidence of MACCEs at 3 years than a shorter regimen (≤1 year) in both patients with and without diabetes.

Interaction Effect Between Hs-CRP and DAPT Duration

To assess whether the benefit of prolonged DAPT in patients with high residual inflammatory risk varies by hs-CRP levels, the interaction between hs-CRP tertiles and DAPT duration was evaluated. No significant interaction was observed for MACCE risk (*P* for interaction = 0.912) or for other secondary outcomes (Supplementary Table 2). This suggests that the cardiovascular benefit of prolonged DAPT was consistent across hs-CRP tertiles among patients with high residual inflammatory risk.

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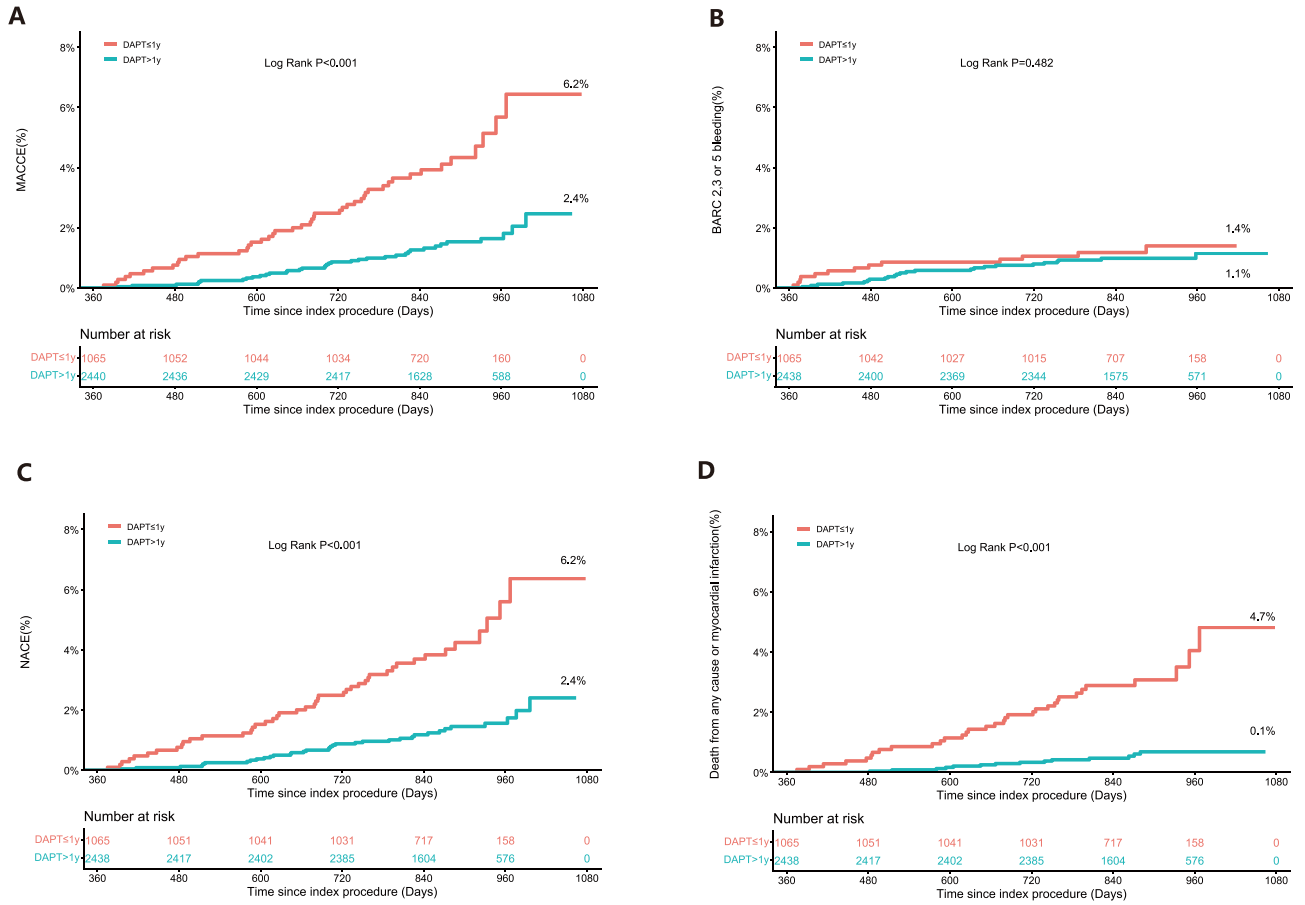

Figure 2 Kaplan-Meier curves for clinical outcomes according to DAPT duration (>1 year vs ≤1 year) in patients with elevated inflammatory status and drug-eluting stent implantation. (**A**) MACCE, (**B**) BARC Type 2, 3, or 5 Bleeding, (**C**) NACE, (**D**) Death from any cause or myocardial infarction.
Abbreviations: DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebrovascular event; NACE, net adverse clinical events.

Discussion

This study, using a large-scale, prospective, real-world registry, investigated the efficacy and safety of extended DAPT duration in 3510 patients with high residual inflammatory risk. The major findings are as follows: (1) Prolonged DAPT (>1 year) was associated with lower risks of MACCEs, NACEs, and the composite endpoint of all-cause death and MI, without increasing the risk of BARC 2, 3, or 5 bleeding within 3 years after PCI in patients with high residual inflammatory risk. (2) Compared with those taking DAPT ≤ 1 year, patients with high residual inflammatory risk taking prolonged DAPT had lower cumulative incidence of all-cause death, death from cardiovascular causes, and definite or probable stent thrombosis over three years. (3) The effect of prolonged DAPT on 3-year MACCEs was consistent with the overall population across most major clinical subgroups. Taken together, these results provide supportive evidence for prolonged DAPT in patients undergoing PCI with high residual inflammatory risk, and inflammatory status may serve as an additional factor for clinicians to consider when deciding the optimal duration of DAPT.

The optimal duration of DAPT for patients after PCI has been a controversial and much-debated topic. An adequate duration of DAPT prevents thrombotic complications of the stented segments, reduces ischemic events, and improves clinical outcomes after coronary stent implantation.[27–29] Evidence suggests that some patients at high ischemic risk will benefit from prolonged DAPT treatment beyond 12 months after PCI, including those with left main coronary artery stenting, chronic total occlusion, or elevated lipoprotein(a) concentrations.[30–32] Results from the DAPT (Dual Antiplatelet Therapy) trial showed that prolonged DAPT was superior to 12-month DAPT for preventing ischemic events after drug-eluting stent (DES) implantation, with lower rates of stent thrombosis and MACCEs in groups receiving continued treatment with thienopyridine and aspirin.[33] Another multi-center randomized trial suggested that

Table 3 Three-year Event Rates of DAPT >12 Months versus DAPT ≤12 Months Between 12 and 36 Months in Patients with High Residual Inflammatory Risk Free of Events at 12 Months After PCI

	Overall (N =3,510)	DAPT ≤1y (N =1,070)	DAPT >1y (N=2,440)	*P* value
Primary endpoint				
MACCE	82 (2.3)	45 (4.2)	37 (1.5)	<0.001
Key safety outcome				
BARC 2, 3, or 5 bleeding	37 (1.1)	13 (1.2)	24 (1.0)	0.661
Major secondary endpoint				
NACE	79 (2.3)	44 (4.1)	35 (1.4)	<0.001
Other secondary endpoints				
Death from any cause or myocardial infarction	47 (1.3)	33 (3.1)	14 (0.6)	<0.001
Death from cardiovascular causes	19 (0.5)	19 (1.8)	0 (0.0)	<0.001
Death from any cause	32 (0.9)	32 (3.0)	0 (0.0)	<0.001
Myocardial infarction	22 (0.6)	8 (0.7)	14 (0.6)	0.712
Target vessel revascularization	62 (1.8)	10 (0.9)	52 (2.1)	0.019
Stent thrombosis, definite or probable	20 (0.6)	15 (1.4)	5 (0.2)	<0.001
Stroke	38 (1.1)	15 (1.4)	23 (0.9)	0.302

Note: Data are n (%).
Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events. NACE, net adverse clinical events.

Table 4 Three-year Clinical Events of DAPT >12 Months Versus DAPT ≤12 Months Between 12 and 36 Months in Patients with High Residual Inflammatory Risk Free of Events at 12 Months After PCI

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary endpoint						
MACCE	0.331(0.214,0.512)	<0.001	0.338(0.219,0.523)	<0.001	0.347(0.224,0.539)	<0.001
Key safety outcome						
BARC 2, 3, or 5 bleeding	0.785(0.4,1.543)	0.483	0.784(0.399,1.541)	0.480	0.793(0.401,1.57)	0.506
Major secondary endpoint						
NACE	0.322(0.207,0.503)	<0.001	0.330(0.211,0.514)	<0.001	0.338(0.216,0.53)	<0.001
Other secondary endpoints						
Death from any cause or myocardial infarction	0.174(0.093,0.326)	<0.001	0.177(0.095,0.332)	<0.001	0.182(0.097,0.341)	<0.001

Notes: Model 1: crude. Model 2: adjusted for age, sex, body mass index. Model 3: Model 2 + diagnosis of diabetes, dyslipidemia, hypertension, chronic kidney disease, history of myocardial infarction, and left ventricular ejection fraction.

Table 5 Subgroup Analysis of the Primary Endpoint According to DAPT Duration

Subgroup	DAPT ≤1y	DAPT >1y	HR (95%CI)	P for Interaction
Age (years)				0.54
<75	37/994	34/2290	0.362(0.226,0.578)	
≥75	8/76	3/150	0.205(0.051,0.817)	
Sex				0.834
Female	10/253	7/573	0.364(0.222,0.596)	
Male	35/817	30/1867	0.315(0.119,0.835)	
Diabetes				0.025
Yes	22/344	10/785	0.175(0.082,0.373)	
No	23/726	27/1655	0.524(0.297,0.923)	

(*Continued*)

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Table 5 (Continued).

Subgroup	DAPT ≤1y	DAPT >1y	HR (95%CI)	P for Interaction
Hypertension				0.824
Yes	36/704	29/1648	0.343(0.209,0.561)	
No	9/366	8/792	0.434(0.161,1.171)	
Dyslipidemia				0.905
Yes	30/698	25/1668	0.350(0.204,0.6)	
No	15/372	12/772	0.316(0.146,0.681)	
CKD				0.734
Yes	5/49	3/93	0.382(0.082,1.79)	
No	40/1021	34/2347	0.338(0.213,0.535)	
History of MI				0.507
Yes	12/147	8/426	0.177(0.083,0.376)	
No	33/923	29/2014	0.528(0.299,0.93)	
Currently smoker				0.267
Yes	29/644	19/1437	0.289(0.161,0.519)	
No	16/426	18/1003	0.453(0.23,0.894)	
Clinical presentation				0.874
ACS	29/729	24/1606	0.349(0.203–0.601)	
CCS	16/341	13/834	0.332(0.155–0.710)	

Abbreviations: CKD, Chronic Kidney Disease. MI, myocardial infarction. ACS, acute coronary syndrome. CCS, chronic coronary syndrome.

patients with acute coronary syndrome receiving 12-month or longer DAPT after current-generation DES implantation had significantly lower MI rates, without a significant difference in major bleeding or BARC 2 to 5 bleeding rates.[34] A previous meta-analysis demonstrated that long-term DAPT (≥12 months) led to significant reductions in MACEs in the complex PCI group, compared with short-term DAPT.[35] Therefore, identifying patients at high ischemic risk is critical to determining who may benefit from the prolonged DAPT strategy.

The primary finding of our study was that, in patients undergoing PCI with high residual inflammatory risk, prolonged DAPT (>12 months) was associated with lower risks of 3-year MACCEs, NACEs, and the composite endpoint of all-cause death and MI, without significantly increasing the risk of BARC 2, 3, or 5 bleeding. This suggests that patients with high residual inflammatory risk may benefit from DAPT for more than 12 months. Similarly, a post hoc analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) study found that adding clopidogrel to aspirin reduced the 1-year composite endpoint (death, MI, or stroke) in patients in the highest two tertiles of hs-CRP after nonurgent PCI with bare metal stents, but not in the lowest tertile.[36] Our study adds to previous evidence from the CREDO substudy that patients after PCI with high residual inflammatory risk are more likely to benefit from prolonged DAPT. The higher 3-year target vessel revascularization rate in the prolonged DAPT group could be partly explained by the higher proportion of patients with left main or multi-vessel coronary artery disease,[37,38] and by the fact that physicians tend to extend DAPT for those with more residual lesions or complex procedures.

The mechanisms underlying the benefits of prolonged DAPT in patients with high residual inflammatory risk remain unclear. Prior studies have indicated that patients undergoing PCI with residual inflammatory risk have worse clinical outcomes, and elevated hs-CRP levels serve as an independent predictor of major adverse cardiovascular events and MACCEs.[15,39,40] Additionally, a series of studies have investigated the relationship between hs-CRP levels and ischemic and bleeding risks in patients after PCI. High hs-CRP levels have been associated with increased ischemic risk, as confirmed by previous studies,[16,41,42] suggesting the need for intensified ischemic risk management after PCI in patients with high residual inflammatory risk. Cook et al also observed that very late thrombosis (>1 year) after DES implantation was associated with histopathological and serological signs of inflammation,[43] which may explain why patients with high residual inflammatory risk benefit from DAPT for more than 1 year. Furthermore, inflammatory conditions influence platelet function and the antiplatelet effect, both of which are closely related to ischemic risk. Jiang et al found that

aspirin and clopidogrel exhibited less effective platelet aggregation inhibition and an unstable antiplatelet effect in patients with high hs-CRP levels[44] Inflammatory status, as depicted by CRP or hs-CRP, has been associated with high platelet reactivity in patients receiving DAPT,[45–47] which has been linked to an increased risk of ischemic events after PCI.[48] Moreover, protein related to platelet aggregation was found to be reduced with colchicine therapy, further validating the modulatory impact of inflammation on platelet function.[49] Accumulating evidence suggests that inflammation and thrombosis share common signaling pathways, and that inflammatory responses can promote activation of the coagulation cascade and stimulate platelet activation.[18] Therefore, continuation of DAPT beyond 1 year may provide benefits from these factors for patients who underwent PCI with high residual inflammatory risk.

Bleeding risk is another crucial factor to consider when determining the duration of DAPT. Although reduced ischemic events are often at the cost of increased bleeding risk from prolonged DAPT, our findings indicated that DAPT for more than 1 year did not significantly increase BARC 2, 3, or 5 bleeding among patients with high residual inflammatory risk. Current studies on bleeding risk in patients with high residual inflammatory risk have yielded conflicting results.[16,41,50] Several studies found there was no association between hs-CRP levels and bleeding risk,[16,41] while other studies observed a higher bleeding risk in those with persistent residual inflammatory risk.[24] Such discrepancy may be explained by different thresholds of hs-CRP level, definitions of bleeding and ethnic factors. It's noteworthy that all participants in our study were prescribed aspirin and clopidogrel because other more potent $P2Y_{12}$ inhibitors were unavailable in China during the study period. And clopidogrel was associated with lower bleeding risk as compared with ticagrelor or prasugrel,[51] so it should take caution before extrapolating our findings to all DAPT regimens. Because the evidence evaluating bleeding risk in patients with high inflammatory risk is relatively limited, a robust conclusion on the safety of prolonged DAPT should be cautiously drawn from further studies.

Subgroup analysis of our study revealed that diabetes appeared to modulate the effect of DAPT on the 3-year MACCE rate in patients with high residual inflammatory risk. Patients with diabetes were more likely to benefit from prolonged DAPT therapy, corroborating previous studies showing that the benefits of extended clopidogrel therapy were more pronounced in diabetic patients receiving DES compared with nondiabetic patients.[52,53] Diabetic patients often have an increased proinflammatory and prothrombotic state, and are more likely to be poor responders to antiplatelet therapy due to higher platelet turnover and pharmacokinetic changes.[54,55] Taken together, these factors may help explain the favorable results of prolonged DAPT therapy in patients with diabetes.

However, the findings of our study should be interpreted cautiously due to several limitations. First, due to the observational, non-randomized nature of this single-center study, it precludes causal inferences and is limited by selection bias and unbalanced baseline characteristics. The duration of DAPT was not predefined but was determined at the discretion of cardiologists. For example, the short-DAPT group had a higher proportion of patients with MI at baseline, reflecting clinicians' preference to prescribe prolonged DAPT to higher-risk patients. Residual confounding from unmeasured factors could not be fully identified despite robust multivariable Cox regression adjustments. The results of our study should be considered hypothesis-generating and further validated by prospective randomized trials. Second, all participants were prescribed clopidogrel and aspirin because ticagrelor and prasugrel were unavailable during the recruitment of our study, which limits the extrapolation of our conclusions to more potent $P2Y_{12}$ inhibitors. Third, our analysis was based on the baseline hs-CRP levels of participants, and the hs-CRP levels during follow-up were unknown, which could have influenced the clinical outcomes. Fourth, given the lower-than-expected event rate, the statistical power of the present analysis may be constrained, increasing the risk of a type II error. Therefore, our findings cannot draw definitive conclusions, and large studies with adequate power are warranted to validate these findings. Fifth, the study population was defined by the PCI procedure rather than by the underlying clinical diagnosis. Patients undergoing primary PCI (for STEMI) and those undergoing elective PCI, inherently with different baseline ischemic risk, were analyzed in the same cohort. While we have reported the distribution of index diagnoses in Table 1, the study was not adequately powered to perform formal subgroup analyses by each diagnostic category or by PCI indication (primary vs. elective). Future prospective studies with larger sample sizes and predefined diagnostic subgroups are needed to validate our findings.

Conclusion

In patients undergoing PCI with high residual inflammatory risk, prolonged DAPT (>1 year) was associated with reduced 3-year MACCE rates, without a significant increase in bleeding risk. Our study suggested that inflammation could be an important factor to consider when deciding the optimal duration of DAPT. Further larger randomized trials with predefined diagnostic subgroups evaluating the efficacy and safety of DAPT for more than 1 year in patients with high residual inflammatory risk are warranted in the future.

Abbreviations

DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; DES, drug-eluting stent; BARC, Bleeding Academic Research Consortium; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular event; NACE, net adverse clinical events; SD, standard deviation; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; CCS, chronic coronary syndrome.

Data Sharing Statement

The data that supports the findings of this study are available from the corresponding author, upon reasonable request.

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Disclosure

The authors declare that they have no competing interests for this study.

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