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ORIGINAL INVESTIGATIONS

Comparison of Antiplatelet Monotherapies After Percutaneous Coronary Intervention According to Clinical, Ischemic, and Bleeding Risks

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ABSTRACT

BACKGROUND Clopidogrel was superior to aspirin monotherapy in secondary prevention after percutaneous coronary intervention (PCI).

OBJECTIVES The purpose of this study was to evaluate the benefits of clopidogrel across high-risk subgroups

METHODS This was a post hoc analysis of the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy) trial that randomly assigned patients who were event free for 6 to 18 months post-PCI on dual antiplatelet therapy (DAPT) to clopidogrel or aspirin monotherapy. Two clinical risk scores were used for risk stratification: the DAPT score and the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P) (the sum of age ≥75 years, diabetes, hypertension, current smoking, peripheral artery disease, stroke, coronary artery bypass grafting, heart failure, and renal dysfunction). The primary composite endpoint was a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission because of acute coronary syndrome, and major bleeding (Bleeding Academic Research Consortium type ≥3) at 2 years after randomization.

RESULTS Among 5,403 patients, clopidogrel monotherapy showed a lower rate of the primary composite endpoint than aspirin monotherapy (HR: 0.73; 95% CI: 0.59-0.90). The benefit of clopidogrel over aspirin was consistent regardless of TRS 2°P (high TRS 2°P [≥3] group: HR: 0.65 [95% CI: 0.44-0.96]; and low TRS 2°P [<3] group: HR: 0.77 [95% CI: 0.60-0.99]) (*P* for interaction = 0.454) and regardless of DAPT score (high DAPT score [≥2] group: HR: 0.68 [95% CI: 0.46-1.00]; and low DAPT score [<2] group: HR: 0.75 [95% CI: 0.59-0.96]) (*P* for interaction = 0.662). The association was similar for the individual outcomes.

CONCLUSIONS The beneficial effect of clopidogrel over aspirin monotherapy was consistent regardless of clinical risk or relative ischemic and bleeding risks compared with aspirin monotherapy. (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis- EXtended Antiplatelet Monotherapy [HOST-EXAM]; NCT02044250) (J Am Coll Cardiol 2023;82:1565-1578) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CV = cardiovascular

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TRS 2°P = Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention

In patients undergoing percutaneous coronary intervention (PCI), an initial dual antiplatelet therapy (DAPT) is the standard treatment to reduce thrombotic complications, and subsequent chronic maintenance of single antiplatelet therapy is recommended for secondary prevention of cardiovascular (CV) events.[1,2] Although aspirin monotherapy has been considered the standard, the recent randomized controlled HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy) trial showed the superiority of clopidogrel to aspirin monotherapy in reducing thrombotic and bleeding events following successful completion of DAPT after PCI.[3,4] Meanwhile, the risk of recurrent CV events is mainly affected by clinical and procedural characteristics,[5] and the current guidelines highlight stratified secondary prevention based on clinical and procedural factors for patients who received revascularization.[1,2] Considering the increasing proportion of high-risk patients who receive PCI and their subsequent sustained risk,[6,7] the incorporation of clinical and procedural risk assessment with the appropriate

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antiplatelet monotherapy for chronic maintenance is needed for effective secondary prevention. In particular, evaluating individual ischemic and bleeding risks is essential for the prevention of ischemic events without inducing unnecessary bleeding with indefinite antiplatelet monotherapy.[8] Therefore, investigating the benefit of clopidogrel over aspirin monotherapy, taking into account the overall clinical risks and the relative ischemic and bleeding risks, is crucial to provide the guide for appropriate antiplatelet monotherapy. In this regard, we performed this study to explore whether the benefits of clopidogrel over aspirin is consistent and maintained in various high clinical risk situations using the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P)[9,10] and the DAPT score.[11-13]

METHODS

STUDY FLOW AND PARTICIPANTS. This study is a post hoc analysis of HOST-EXAM (NCT02044250), which was an investigator-initiated, prospective, randomized, open-labeled, and multicenter trial conducted at 37 study sites in the Republic of Korea. The detailed study protocol and inclusion/exclusion criteria of the trial have been described previously.[3,14] Briefly, patients who underwent PCI with drug-eluting stents (DES) and maintained DAPT after PCI without clinical events for 6 to 18 months were included. There was no restriction on the diagnosis at the index PCI and procedural characteristics for inclusion in the trial. The main exclusion criteria included patients with known hypersensitivity or contraindications for clopidogrel and those who should maintain their current DAPT regimen for any reason. DAPT before enrollment consisted of aspirin and any $P2Y_{12}$ inhibitor. After enrollment, all patients who met the inclusion criteria and had no exclusion criteria were randomized to the clopidogrel group (75 mg once daily) or aspirin group (100 mg once daily) in a 1:1 ratio. Among 5,438 randomized between March 26, 2014, and May 29, 2018, 5,403 patients who had full information on clinical risk factors and the DAPT score were included in the current study (Supplemental Figure 1). The study protocol was approved by the Institutional Review Board at each participating center. All participants provided written informed consent at the time of enrollment and randomization. The data and safety monitoring board examined the safety of the patients. The Seoul National University Hospital Clinical Trial Center and Medical Research Collaborating Center performed the scientific conduct of the trial, data management, and independent data analysis. This study was done following the standards specified in the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

DEFINITIONS OF CLINICAL OUTCOMES. Clinical follow-up was scheduled at 12 and 24 months with a window of ±3 months. Any additional visits were at the discretion of the treating physicians. Active surveillance for any adverse clinical events and the evaluation of adherence to the antiplatelet monotherapy were performed at each visit. In the HOST-EXAM trial, the primary composite endpoint was defined as a composite of all-cause death, nonfatal myocardial infarction (MI), stroke, readmission because of acute coronary syndrome, and major

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bleeding events (Bleeding Academic Research Consortium [BARC] type ≥3). The secondary endpoints were major bleeding and the thrombotic composite endpoint, a composite of cardiac death, MI, ischemic stroke, readmission because of acute coronary syndrome, and definite or probable stent thrombosis.[3,4] All clinical events were adjudicated by an independent event adjudication committee blinded to the trial group assignments. The vital status of each patient was cross-verified using the National Health Insurance Service system of South Korea and the South Korean National Statistics System.

CLINICAL RISK ASSESSMENT. The TRS 2°P was used for clinical risk stratification.[5,9,10] Briefly, TRS 2°P was developed for risk prediction of patients with known coronary artery disease. TRS 2°P was calculated by the sum of 9 factors: age ≥75 years, diabetes, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2). Patients were grouped into high and low clinical groups according to the TRS 2°P ≥3 based on the prior publications.[9,15]

DAPT SCORE ASSESSMENT. The DAPT score was developed to estimate the risk of both ischemic events and bleeding. It is comprised of 9 variables, including age, smoking, diabetes, MI presentation, prior history of PCI or MI, paclitaxel-eluting stent, stent diameter <3 mm, congestive heart failure of left ventricular ejection fraction <30%, and vein graft stent.[11] The score ranges from −2 to 10, and the event rate of MI, definite or probable stent thrombosis, and major bleeding was tested according to the DAPT score in accordance with the DAPT score study[11] to explore the discrimination of ischemic and bleeding risks in the current study population by the DAPT score. The study population was stratified into high DAPT score (≥2), who had a higher ischemic risk than bleeding risk, and low DAPT score (<2), who showed a higher bleeding risk than ischemic risk, based on the prior publication.[11]

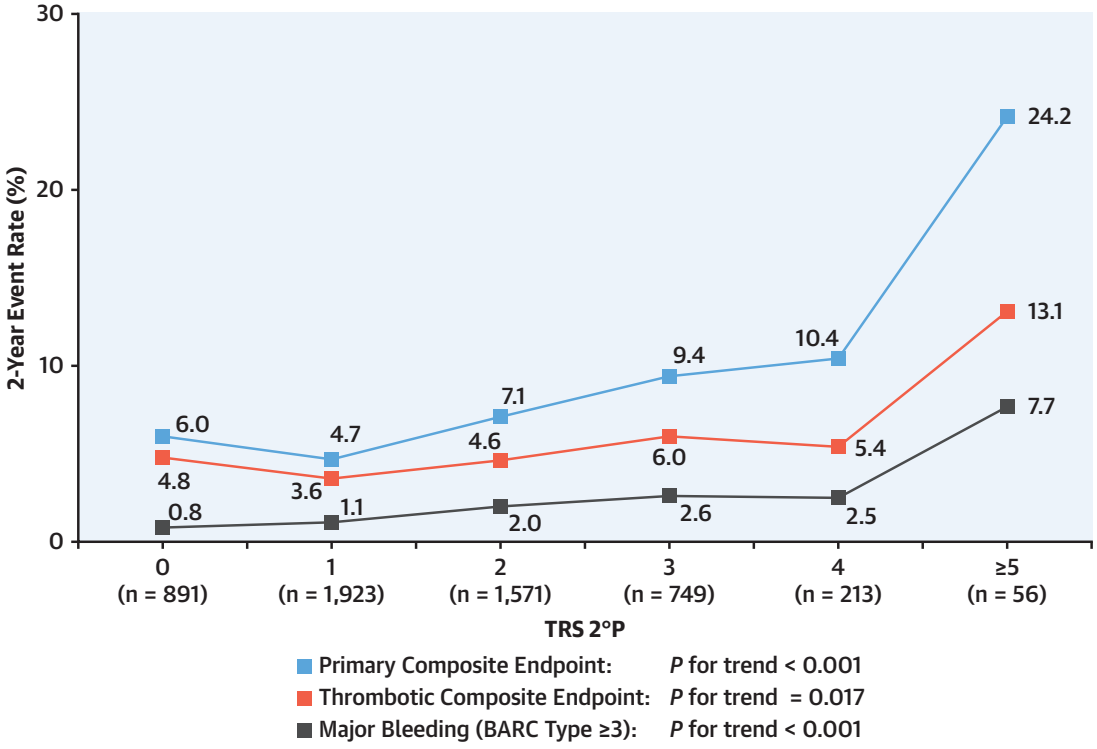
STATISTICAL ANALYSIS. Categorical variables were expressed as numbers (%) and continuous variables as mean ± SD or median (IQR) according to the normality distribution. The Shapiro-Wilk test normality test was used to determine the normality of variables. In the comparison of variables between groups, the chi-square test was used for categorical variables, and the Student's *t*-test or the Wilcoxon rank-sum test was used for continuous variables as appropriate. Cumulative events of the clinical outcomes were compared between groups using Kaplan-Meier censoring estimates and the log-rank test. The chi-square test for trend in proportions was performed to evaluate the significance of trends. Cox proportional hazard model was applied to estimate the corresponding HR with a 95% CI. In multivariable analyses, variables with a significant association with the primary composite endpoint among patient and procedural characteristics were included as covariates. The assumption of the Cox proportional hazard model was evaluated by Schoenfeld residuals. A Bayesian analysis was performed where the probabilities of relative risk between clopidogrel vs aspirin arms were calculated according to the TRS 2°P and the DAPT score for the thrombotic composite endpoints and major bleeding. *P* values of <0.05 were considered significant. All analyses were performed using R language version 4.1.0 (R Foundation for Statistical Computing).

RESULTS

DISTRIBUTION OF RANDOMIZED PATIENTS AND CLINICAL OUTCOMES IN THE TOTAL POPULATION. Baseline clinical characteristics are presented in Supplemental Table 1. Among a total of 5,403 patients, the median age was 64.0 years (IQR: 56.0-72.0 years), and 74.7% of patients were male. Multivessel disease was present in 49.6% of patients, and complex PCI was performed in 22.1% of patients. When classified by TRS 2°P, the distribution of patients was 16.5%, 35.6%, 29.1%, 13.9%, 3.9%, and 1.0% for TRS 2°P of 0, 1, 2, 3, 4, and ≥5, respectively (Supplemental Figure 2). This distribution was similar between the aspirin and clopidogrel arms (Supplemental Figure 2). When stratified by the DAPT score, the distribution of patients was 2.7%, 11.7%, 24.6%, 26.7%, 20.7%, and 13.6% for DAPT scores of −2, −1, 0, 1, 2, and ≥3 and was similar between the aspirin and clopidogrel arms (Supplemental Figure 3). During the follow-up, the primary composite endpoint occurred in 357 (6.6%) patients, the thrombotic composite endpoint in 243 patients (4.5%), and major bleeding in 86 (1.6%) patients. In the total population, clopidogrel monotherapy was associated with a lower risk of the primary composite endpoint (HR: 0.73; 95% CI: 0.59-0.90; $P = 0.003$), the thrombotic composite endpoint (HR: 0.68; 95% CI: 0.52-0.87; $P = 0.003$), and major bleeding (HR: 0.63; 95% CI: 0.41-0.97; $P = 0.035$), compared with aspirin monotherapy.

OUTCOME COMPARISON BETWEEN CLOPIDOGREL AND ASPIRIN ARMS ACCORDING TO THE TRS 2°P. As the TRS 2°P increased (TRS 2°P of 0, 1, 2, 3, 4, and ≥5, respectively), the rate of the primary composite

FIGURE 1 Trends of Clinical Outcomes According to the TRS 2°P



The outcome trends of the primary composite endpoint, the thrombotic endpoint, and major bleeding (Bleeding Academic Research Consortium [BARC] type ≥3) according to the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P) are shown. The definition of the primary endpoint is a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission because of acute coronary syndrome, and major bleeding events (BARC type ≥3). The definition of the thrombotic composite endpoint is a composite of cardiac death, myocardial infarction, ischemic stroke, readmission because of acute coronary syndrome, and definite or probable stent thrombosis.

endpoint increased (6.0%, 4.7%, 7.1%, 9.4%, 10.4%, and 24.2%, respectively; *P* for trend <0.001), the rate of the thrombotic composite endpoint increased (4.8%, 3.6%, 4.6%, 6.0%, 5.4%, and 13.1%, respectively; *P* for trend = 0.017), and the rate of major bleeding increased (0.8%, 1.1%, 2.0%, 2.6%, 2.5%, and 7.7%, respectively; *P* for trend <0.001) (Figure 1). When grouped into high (≥3) and low (<3) TRS 2°P, 1,018 (18.8%) patients had high TRS 2°P, whereas 4,385 (81.2%) patients had low TRS 2°P. Within the high- and low-TRS 2°P groups, 50.1% and 48.6% received clopidogrel monotherapy, and overall clinical characteristics and laboratory findings were well balanced between the aspirin and clopidogrel arms in both high and low TRS 2°P groups, except for low-density lipoprotein cholesterol level in the low-TRS 2°P group (Table 1). When clinical outcomes were compared between aspirin and clopidogrel according to the TRS 2°P, the trends for the beneficial effect of clopidogrel were consistent for the primary composite endpoint (HR: 0.65; 95% CI: 0.44-0.96; *P* = 0.032 in the high TRS 2°P group; HR: 0.77; 95% CI: 0.60-0.99; *P* = 0.042 in the low TRS 2°P group) (*P* for interaction = 0.454) (Figure 2). This result was similar for the thrombotic composite endpoint and major bleeding (Supplemental Figure 4) and individual outcome components without significant interaction (Table 2).

CLINICAL OUTCOMES AFTER CLOPIDOGREL VS ASPIRIN MONOTHERAPY IN THE HIGH- AND LOW-DAPT SCORE GROUPS. As the DAPT score increased (DAPT score of −2, −1, 0, 1, 2, and ≥3, respectively), the rate of MI increased (0.0%, 1.0%, 0.6%, 0.7%, 0.9%, 1.7%, respectively; *P* for trend = 0.044), whereas the rate of major bleeding decreased (2.9%, 2.6%, 1.8%, 1.4%, 1.1%, and 1.4%, respectively; *P* for trend = 0.015) (Figure 3). When classified into high (≥2) and low (<2) DAPT score, 1,854 (34.3%) patients had high DAPT score, whereas 3,549 (65.7%) patients had low DAPT score. In the high- and low-DAPT score groups, 50.4% and 48.7%

TABLE 1 Baseline Characteristics Stratified by Antiplatelet Monotherapy and the TRS 2°P

	Low (<3) TRS 2°P (n = 4,385)			High (≥3) TRS 2°P (n = 1,018)		
	Aspirin (n = 2,189)	Clopidogrel (n = 2,196)	*P* Value	Aspirin (n = 523)	Clopidogrel (n = 495)	*P* Value
Clinical characteristics						
Age, y	62.0 (55.0-69.0)	62.0 (55.0-69.0)	0.840	73.0 (62.0-79.0)	75.0 (63.0-78.0)	0.319
Male	1,679 (76.7)	1,684 (76.7)	1.000	348 (66.5)	323 (65.3)	0.714
Diabetes	525 (24.0)	554 (25.2)	0.357	406 (77.6)	365 (73.7)	0.169
Hypertension	1,176 (53.7)	1,197 (54.5)	0.623	487 (93.1)	458 (92.5)	0.807
Dyslipidemia	1,493 (68.2)	1,487 (67.7)	0.752	381 (72.8)	382 (77.2)	0.129
Current smoker	409 (18.7)	384 (17.5)	0.322	171 (32.7)	161 (32.5)	1.000
Previous cerebrovascular accident	50 (2.3)	43 (2.0)	0.519	82 (15.7)	77 (15.6)	1.000
Previous peripheral artery disease	10 (0.5)	14 (0.6)	0.544	22 (4.2)	22 (4.4)	0.974
Previous heart failure	39 (1.8)	39 (1.8)	1.000	76 (14.5)	69 (13.9)	0.857
Chronic kidney disease	91 (4.2)	104 (4.7)	0.392	242 (46.3)	249 (50.3)	0.221
Clinical diagnosis at the index PCI			0.498			0.477
Silent ischemia	58 (2.6)	43 (2.0)		12 (2.3)	15 (3.0)	
Stable angina	553 (25.3)	551 (25.1)		144 (27.5)	127 (25.7)	
Unstable angina	766 (35.0)	802 (36.5)		185 (35.4)	169 (34.1)	
NSTEMI	429 (19.6)	413 (18.8)		97 (18.5)	112 (22.6)	
STEMI	383 (17.5)	387 (17.6)		85 (16.3)	72 (14.5)	
DAPT duration	380.0 (357.0-419.0)	383.0 (357.0-423.5)	0.286	382.0 (361.0-427.0)	383.5 (357.0-424.0)	0.534
Laboratory findings						
White blood cells, cells/μL	6.5 (5.4-7.7)	6.4 (5.4-7.6)	0.323	6.9 (5.9-8.4)	6.8 (5.5-8.3)	0.059
Hemoglobin, g/dL	14.1 (13.0-15.0)	14.1 (13.0-15.0)	0.811	13.1 (11.6-14.4)	12.9 (11.2-14.2)	0.053
Creatinine, mg/dL	0.90 (0.78-1.00)	0.90 (0.77-1.01)	0.759	1.06 (0.88-1.34)	1.10 (0.90-1.38)	0.219
Total cholesterol, mg/dL	136.0 (119.0-154.0)	135.0 (117.0 154.0)	0.164	129.0 (114.0-151.0)	131.2 (109.0-149.0)	0.470
Triglyceride, mg/dL	106.0 (78.0-148.0)	105.0 (77.0-148.0)	0.924	120.5 (86.0-161.0)	112.0 (86.0-150.0)	0.166
HDL cholesterol, mg/dL	45.0 (38.0-53.0)	45.0 (38.0-53.0)	0.714	43.0 (37.0-51.0)	42.0 (35.7-52.0)	0.736
LDL cholesterol, mg/dL	71.0 (57.1-84.0)	69.0 (55.0-84.0)	0.044	66.0 (52.0-82.0)	63.0 (50.0-80.0)	0.130
Procedural characteristics						
Extent of disease			0.898			0.292
1-vessel disease	1,164 (53.2)	1,153 (52.5)		203 (38.8)	201 (40.6)	
2-vessel disease	676 (30.9)	685 (31.2)		163 (31.2)	167 (33.7)	
3-vessel disease	349 (15.9)	358 (16.3)		157 (30.0)	127 (25.7)	
Complex PCI	462 (21.2)	474 (21.6)	0.738	131 (25.1)	124 (25.2)	1.000
Left main disease	99 (4.5)	105 (4.8)	0.738	31 (5.9)	36 (7.3)	0.460
PCI for bifurcation lesion	238 (10.9)	235 (10.7)	0.893	57 (10.9)	50 (10.1)	0.755
PCI for CTO lesion	208 (9.5)	208 (9.5)	1.000	45 (8.6)	49 (9.9)	0.545
Mean diameter of implanted stents, mm	3.0 (2.8-3.5)	3.0 (2.8-3.5)	0.476	3.0 (2.8-3.3)	3.0 (2.8-3.2)	0.165
Minimum diameter of implanted stents, mm	3.0 (2.8-3.5)	3.0 (2.5-3.5)	0.765	3.0 (2.5-3.0)	2.8 (2.5-3.0)	0.217
Total length of implanted stents, mm	28.0 (18.0-41.0)	28.0 (18.0-43.0)	0.381	32.0 (20.0-50.0)	30.0 (20.0-51.0)	0.743

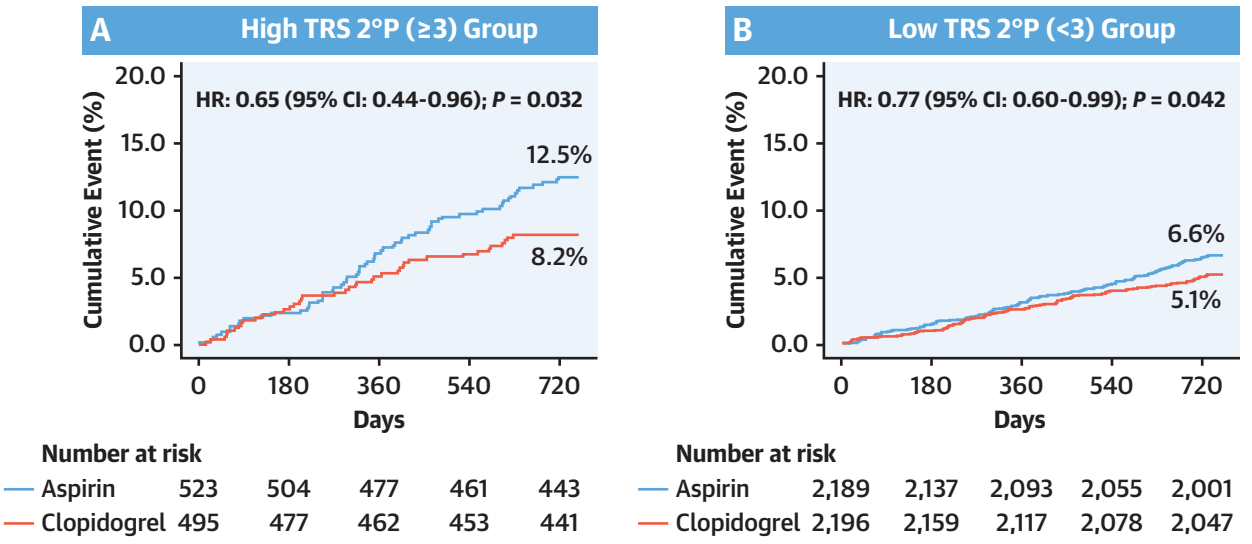
Values are median (IQR) or n (%).

CTO = chronic total occlusion; DAPT = dual antiplatelet therapy; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TRS 2°P = Thrombolysis In Myocardial Infarction risk score for secondary prevention.

received clopidogrel monotherapy, respectively. Overall clinical characteristics and laboratory findings were not different between the aspirin and clopidogrel arms within high- and low-DAPT score groups, except for low-density lipoprotein cholesterol level in the low DAPT score group (Table 3). The lower event rate of the primary endpoint in the clopidogrel arm was consistent in the high-DAPT score group (HR: 0.68; 95% CI: 0.46-1.00; $P = 0.051$) and in the low-DAPT score group (HR: 0.75; 95% CI: 0.59-0.96; $P = 0.025$) without significant interaction (P for interaction = 0.662) (Figure 4). This trend was similarly observed for the thrombotic composite endpoint and major bleeding (Supplemental Figure 5) and individual outcome components with no interaction (Table 4).

RELATIVE RISK FOR THROMBOTIC AND BLEEDING OUTCOMES AFTER CLOPIDOGREL VS ASPIRIN MONOTHERAPY ACCORDING TO CLINICAL RISK AND THE DAPT SCORE. The risk for the thrombotic composite endpoint and major bleeding was individually estimated by a Bayesian analysis (Figure 5).

FIGURE 2 Primary Composite Endpoint Within High and Low TRS 2°P Groups



The cumulative event of the primary composite endpoint was compared between aspirin and clopidogrel arms **(A)** in the high clinical risk group (Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention [TRS 2°P] ≥3) and **(B)** in the low clinical risk group (TRS 2°P <3). The definition of the primary composite endpoint is as in Figure 1.

The RR (clopidogrel/aspirin) for the thrombotic composite endpoint and major bleeding was 0.69 (95% credible interval: 0.38-1.04) and 0.47 (95% credible interval: 0.15-0.86) respectively, in the high-TRS 2°P group, and was 0.70 (95% credible interval: 0.51-0.91) and 0.79 (95% credible interval: 0.41-1.20) respectively, in the low-TRS 2°P group. According to the DAPT score, the RR (clopidogrel/

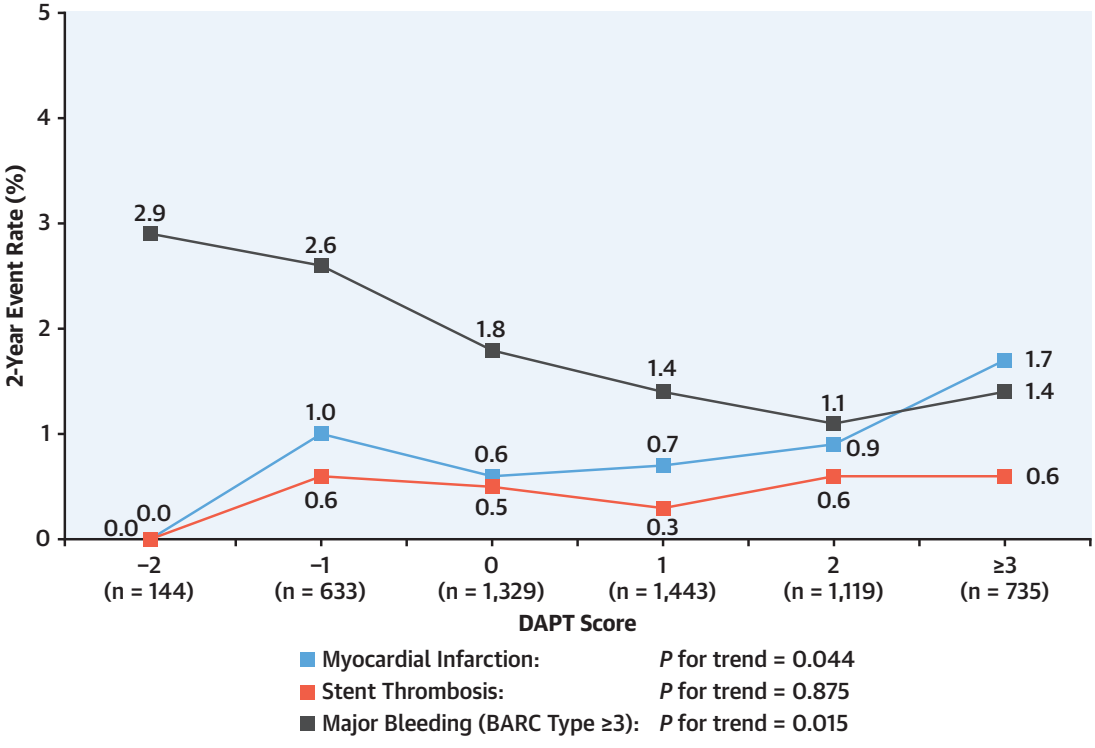
TABLE 2 Clinical Outcomes According to Antiplatelet Monotherapy and the TRS 2°P

	Low (<3) TRS 2°P (n = 4,385)				High (≥3) TRS 2°P (n = 1,018)				
	Aspirin (n = 2,189)	Clopidogrel (n = 2,196)	HR (95% CI)	*P* Value	Aspirin (n = 523)	Clopidogrel (n = 495)	HR (95% CI)	*P* Value	*P* Value for Interaction
Primary composite endpoint	142 (6.6)	111 (5.1)	0.77 (0.60-0.99)	0.042	64 (12.5)	40 (8.2)	0.65 (0.44-0.96)	0.032	0.454
Thrombotic composite endpoint	107 (5.0)	74 (3.4)	0.68 (0.51-0.92)	0.012	38 (7.5)	24 (5.0)	0.66 (0.40-1.10)	0.115	0.911
Major bleeding (BARC type ≥3)	33 (1.5)	25 (1.2)	0.76 (0.45-1.27)	0.289	20 (3.9)	8 (1.7)	0.42 (0.19-0.96)	0.039	0.239
All-cause death	18 (0.8)	27 (1.2)	1.50 (0.82-2.72)	0.186	18 (3.5)	24 (4.9)	1.42 (0.77-2.61)	0.263	0.904
Cardiac death	7 (0.3)	8 (0.4)	1.14 (0.41-3.14)	0.801	7 (1.4)	11 (2.3)	1.67 (0.65-4.30)	0.291	0.589
Noncardiac death	11 (0.5)	19 (0.9)	1.72 (0.82-3.62)	0.151	11 (2.2)	13 (2.7)	1.26 (0.56-2.81)	0.574	0.574
Myocardial infarction	22 (1.0)	16 (0.7)	0.72 (0.38-1.38)	0.327	7 (1.4)	1 (0.2)	0.15 (0.02-1.23)	0.077	0.160
Stroke	26 (1.2)	15 (0.7)	0.57 (0.30-1.08)	0.087	17 (3.4)	3 (0.6)	0.19 (0.05-0.63)	0.007	0.109
Hemorrhagic stroke	8 (0.4)	4 (0.2)	0.50 (0.15-1.66)	0.256	9 (1.8)	0 (0.0)	NA	0.004	0.997
Ischemic stroke	18 (0.8)	11 (0.5)	0.61 (0.29-1.29)	0.193	8 (1.6)	3 (0.6)	0.40 (0.11-1.50)	0.172	0.583
Readmission because of acute coronary syndrome	83 (3.9)	55 (2.5)	0.66 (0.47-0.92)	0.016	25 (4.9)	10 (2.1)	0.42 (0.20-0.88)	0.021	0.283
Definite or probable stent thrombosis	11 (0.5)	8 (0.4)	0.73 (0.29-1.80)	0.489	5 (1.0)	1 (0.2)	0.21 (0.02-1.81)	0.156	0.301
Any bleeding (BARC type ≥2)	56 (2.6)	46 (2.1)	0.82 (0.55-1.21)	0.312	31 (6.1)	15 (3.1)	0.51 (0.27-0.94)	0.032	0.202

Values are n (%) (cumulative events) unless otherwise indicated. The primary composite endpoint is defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission because of acute coronary syndrome, and major bleeding events (Bleeding Academic Research Consortium [BARC] type ≥3). The thrombotic composite endpoint was defined as a composite of cardiac death, myocardial infarction, ischemic stroke, readmission because of acute coronary syndrome, and definite or probable stent thrombosis.

TRS 2°P = Thrombolysis In Myocardial Infarction risk score for secondary prevention.

FIGURE 3 Trends of Clinical Outcomes According to the DAPT Score



The outcome trends of myocardial infarction, stent thrombosis, and major bleeding (Bleeding Academic Research Consortium [BARC] type ≥3) according to the dual antiplatelet therapy (DAPT) score are shown.

aspirin) for the thrombotic composite endpoint and major bleeding was 0.63 (95% credible interval: 0.35-0.92), and 0.96 (95% credible interval: 1.30-1.79), respectively, in the high-DAPT score group, and was 0.72 (95% credible interval: 0.52-0.94) and 0.58 (95% credible interval: 0.31-0.87), respectively, in the low-DAPT score group.

In the sensitivity analysis, the outcome trend between clopidogrel vs aspirin was consistent after adjustment for significant covariates (Supplemental Table 2) across the high- and low-TRS 2°P groups (Supplemental Table 3) and the high- and low-DAPT score groups (Supplemental Table 4). The results for clinical outcomes were similar after adjustment for high bleeding risk (Supplemental Tables 5 and 6). Overall findings were similarly maintained with 5-year outcomes from the HOST-EXAM extended data (Supplemental Figures 6 to 8).

When patients were classified by the duration of DAPT before randomization, the proportions of patients with a DAPT duration of 6 to 9 months, 9 to 12 months, 12 to 15 months, and 15 to 18 months were 5.4%, 22.4%, 55.1%, and 17.1%, respectively. The DAPT score was higher in patients with a longer DAPT duration, whereas TRS 2°P was similar across the groups (Supplemental Table 7). However, there were no statistical differences in clinical outcomes between patients with a DAPT duration of 6 to 12 months and those with a DAPT duration of 12 to 18 months (Supplemental Table 8), and the DAPT duration was balanced between the aspirin and clopidogrel arms (Supplemental Table 9). In the sensitivity analysis, the benefit of clopidogrel was consistent across high and low DAPT score and TRS 2°P in both the 6- to 12-month DAPT group and the 12- to 18-month DAPT group (Supplemental Figure 9).

DISCUSSION

This post hoc analysis of the HOST-EXAM trial (where patients were randomized to clopidogrel or aspirin after successful DAPT therapy following PCI) investigated the clinical outcomes of clopidogrel vs aspirin monotherapy according to clinical risk using the TRS

TABLE 3 Baseline Characteristics Stratified by Antiplatelet Monotherapy and the DAPT Score

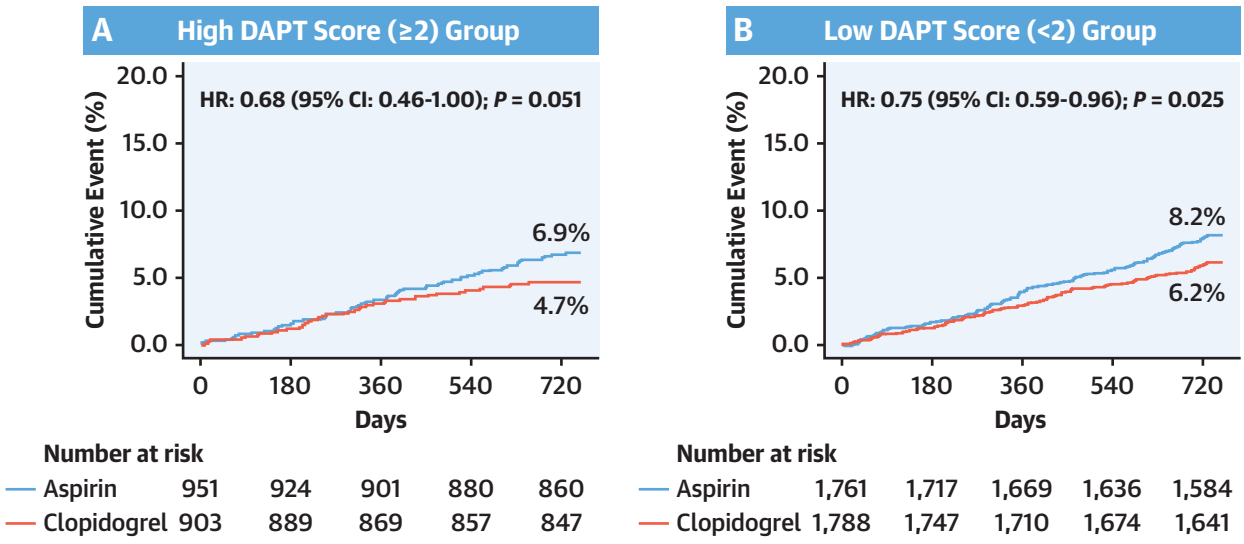
	Low (<2) DAPT Score (n = 3,549)			High (≥2) DAPT Score (n = 1,854)		
	Aspirin (n = 1,761)	Clopidogrel (n = 1,788)	*P* Value	Aspirin (n = 951)	Clopidogrel (n = 903)	*P* Value
Clinical characteristics						
Age, y	68.0 (60.0-74.0)	67.0 (59.0-74.0)	0.442	58.0 (52.0-63.0)	58.0 (52.0-63.0)	0.586
Male	1,202 (68.3)	1,248 (69.8)	0.339	825 (86.8)	759 (84.1)	0.114
Diabetes	453 (25.7)	448 (25.1)	0.675	478 (50.3)	471 (52.2)	0.441
Hypertension	1,120 (63.6)	1,143 (63.9)	0.867	543 (57.1)	512 (56.7)	0.900
Dyslipidemia	1,207 (68.5)	1,227 (68.6)	0.986	667 (70.1)	642 (71.1)	0.687
Current smoker	163 (9.3)	154 (8.6)	0.540	417 (43.8)	391 (43.3)	0.848
Previous cerebrovascular accident	87 (4.9)	82 (4.6)	0.677	45 (4.7)	38 (4.2)	0.665
Previous peripheral artery disease	19 (1.1)	28 (1.6)	0.262	13 (1.4)	8 (0.9)	0.448
Previous heart failure	17 (1.0)	23 (1.3)	0.455	98 (10.3)	85 (9.4)	0.572
Chronic kidney disease	239 (13.6)	253 (14.1)	0.653	94 (9.9)	100 (11.1)	0.447
Clinical diagnosis at the index PCI			0.521			0.705
Silent ischemia	54 (3.1)	46 (2.6)		16 (1.7)	12 (1.3)	
Stable angina	575 (32.7)	549 (30.7)		122 (12.8)	129 (14.3)	
Unstable angina	775 (44.0)	815 (45.6)		176 (18.5)	156 (17.3)	
NSTEMI	197 (11.2)	198 (11.1)		329 (34.6)	327 (36.2)	
STEMI	160 (9.1)	180 (10.1)		308 (32.4)	279 (30.9)	
DAPT duration	380.0 (356.0-421.0)	381.0 (355.5-421.0)	0.929	380.5 (361.0-420.0)	386.0 (360.0-427.0)	0.177
Laboratory findings						
White blood cells, cells/μL	6.3 (5.4-7.5)	6.2 (5.3-7.4)	0.281	7.1 (5.9-8.4)	6.9 (5.8-8.3)	0.160
Hemoglobin, g/dL	13.7 (12.6-14.7)	13.7 (12.5-14.8)	0.499	14.4 (13.3-15.3)	14.3 (13.2-15.2)	0.394
Creatinine, mg/dL	0.90 (0.78-1.05)	0.90 (0.79-1.06)	0.363	0.94 (0.80-1.07)	0.92 (0.80-1.08)	0.200
Total cholesterol, mg/dL	135.0 (118.0-154.0)	134.5 (117.0-153.0)	0.280	134.0 (118.0-153.0)	133.0 (115.0-153.0)	0.318
Triglyceride, mg/dL	104.0 (77.0-142.0)	102.0 (76.0-142.0)	0.516	118.0 (85.0-163.5)	117.0 (84.0-162.5)	0.967
HDL cholesterol, mg/dL	45.1 (39.0-54.0)	46.0 (39.0-54.1)	0.799	43.0 (37.0-50.0)	42.0 (36.0-50.0)	0.140
LDL cholesterol, mg/dL	70.0 (56.0-84.0)	67.0 (54.0-83.0)	0.044	70.0 (57.0-84.0)	70.0 (54.0-84.0)	0.205
Procedural characteristics						
Extent of disease			0.791			0.599
1-vessel disease	914 (51.9)	943 (52.7)		453 (47.6)	411 (45.5)	
2-vessel disease	534 (30.3)	542 (30.3)		305 (32.1)	310 (34.3)	
3-vessel disease	313 (17.8)	303 (16.9)		193 (20.3)	182 (20.2)	
Complex PCI	351 (19.9)	350 (19.6)	0.822	242 (25.7)	248 (27.7)	0.355
Left main disease	87 (4.9)	99 (5.5)	0.470	43 (4.5)	42 (4.7)	0.982
PCI for bifurcation lesion	185 (10.5)	170 (9.5)	0.350	110 (11.6)	115 (12.7)	0.485
PCI for CTO lesion	147 (8.3)	151 (8.4)	0.965	106 (11.1)	106 (11.7)	0.743
Mean diameter of implanted stents, mm	3.0 (2.8-3.5)	3.0 (2.8-3.5)	0.928	2.9 (2.8-3.2)	2.9 (2.8-3.2)	0.829
Minimum diameter of implanted stents, mm	3.0 (2.8-3.5)	3.0 (2.8-3.5)	1.000	2.8 (2.5-3.0)	2.8 (2.5-3.0)	0.539
Total length of implanted stents, mm	28.0 (18.0-40.0)	28.0 (18.0-41.0)	0.869	28.0 (20.0-48.0)	30.0 (22.0-51.0)	0.338

Values are median (IQR) or n (%).
Abbreviations as in Table 1.

2°P and relative ischemic/bleeding risk using the DAPT score. First, rates of the primary outcome increased with a higher TRS 2°P. With an increment of the DAPT score, the rate of MI increased, whereas the rate of major bleeding decreased. Second, better outcomes after clopidogrel monotherapy compared with aspirin monotherapy were consistently observed across the high TRS 2°P (≥3) and the low TRS 2°P (<3) groups. Third, the benefit of clopidogrel was also consistent in patients with high DAPT score (≥2) and low DAPT score (<2), suggesting consistent and sustained benefits of clopidogrel regardless of various clinical risk (**Central Illustration**).

Clinical and procedural risk factors are the main determinants of the risk for recurrent CV events in patients with established CV disease, especially in the long term.[16,17] Given that patients with CV disease are commonly complicated by multiple comorbidities,

FIGURE 4 Primary Composite Endpoint Within High and Low DAPT Score Groups



The cumulative event of the primary composite endpoint was compared between aspirin and clopidogrel arms **(A)** in the high-dual antiplatelet therapy (DAPT) score group (≥2) and **(B)** in the low-DAPT score group (<2). The definition of the primary composite endpoint is as in Figure 1.

integrative risk estimation with various clinical and procedural risk factors is required for secondary prevention.[1,2] TRS 2°P is a simplified risk assessment tool that has been developed and validated to predict the risk for recurrent events of CV patients in whom secondary preventive measures are needed.[9] Although TRS 2°P was not originally developed for risk stratification in patients undergoing PCI, subsequent studies have reported the prognostic value of TRS 2°P after PCI especially for long-term secondary prevention,[5,18] which was also observed for both thrombotic and bleeding outcomes in the current study. As for evaluating ischemic and bleeding risks, the DAPT score is one of the robust risk scores that can account for both ischemic and bleeding risk factors, presenting a higher ischemic risk in a high DAPT score (≥2), whereas a higher bleeding risk is predicted by a low (<2) DAPT score.[11,13] In the current study, the

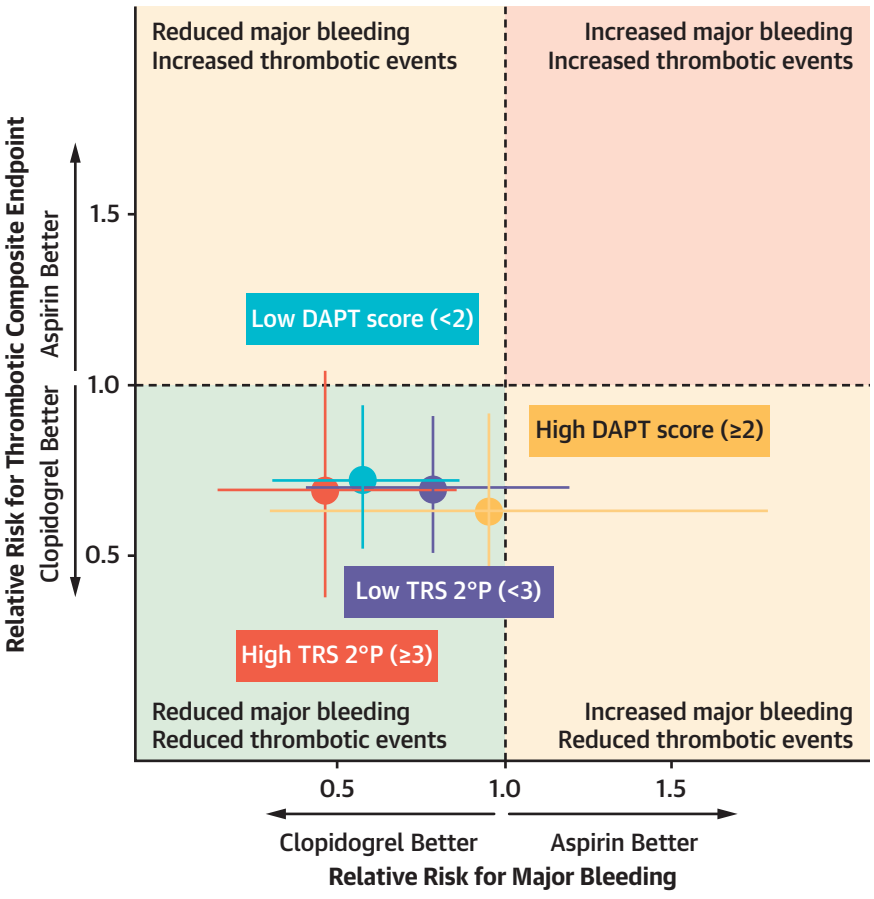
TABLE 4 Clinical Outcomes According to Antiplatelet Monotherapy and the DAPT Score

	Low (<2) DAPT Score (n = 3,549)				High (≥2) DAPT Score (n = 1,854)				
	Aspirin (n = 1,761)	Clopidogrel (n = 1,788)	HR (95% CI)	*P* Value	Aspirin (n = 951)	Clopidogrel (n = 903)	HR (95% CI)	*P* Value	*P* Value for Interaction
Primary composite endpoint	142 (8.2)	109 (6.2)	0.75 (0.59-0.96)	0.025	64 (6.9)	42 (4.7)	0.68 (0.46-1.00)	0.051	0.662
Thrombotic composite endpoint	98 (5.7)	71 (4.1)	0.71 (0.52-0.97)	0.030	47 (5.1)	27 (3.0)	0.59 (0.37-0.95)	0.031	0.520
Major bleeding (BARC type ≥3)	41 (2.4)	23 (1.3)	0.55 (0.33-0.92)	0.024	12 (1.3)	10 (1.1)	0.87 (0.38-2.01)	0.744	0.369
All-cause death	24 (1.4)	39 (2.2)	1.61 (0.97-2.68)	0.065	12 (1.3)	12 (1.3)	1.04 (0.47-2.32)	0.920	0.366
Cardiac death	9 (0.5)	13 (0.7)	1.43 (0.61-3.35)	0.407	5 (0.5)	6 (0.7)	1.25 (0.38-4.09)	0.713	0.854
Noncardiac death	15 (0.9)	26 (1.5)	1.72 (0.91-3.25)	0.094	7 (0.8)	6 (0.7)	0.89 (0.30-2.66)	0.839	0.308
Myocardial infarction	14 (0.8)	10 (0.6)	0.71 (0.31-1.60)	0.406	15 (1.6)	7 (0.8)	0.48 (0.20-1.19)	0.113	0.538
Stroke	30 (1.7)	13 (0.7)	0.43 (0.22-0.82)	0.011	13 (1.4)	5 (0.6)	0.40 (0.14-1.12)	0.082	0.914
Hemorrhagic stroke	12 (0.7)	4 (0.2)	0.33 (0.11-1.02)	0.055	5 (0.5)	0 (0.0)	NA	0.028	0.997
Ischemic stroke	18 (1.0)	9 (0.5)	0.49 (0.22-1.10)	0.084	8 (0.9)	5 (0.6)	0.65 (0.21-1.99)	0.451	0.696
Readmission because of acute coronary syndrome	73 (4.2)	49 (2.8)	0.66 (0.46-0.95)	0.026	35 (3.8)	16 (1.8)	0.47 (0.26-0.85)	0.013	0.338
Definite or probable stent thrombosis	9 (0.5)	6 (0.3)	0.66 (0.24-1.86)	0.433	7 (0.8)	3 (0.3)	0.45 (0.12-1.73)	0.242	0.650
Any bleeding (BARC type ≥2)	66 (3.8)	42 (2.4)	0.63 (0.43-0.92)	0.018	21 (2.3)	19 (2.1)	0.94 (0.51-1.76)	0.857	0.272

Values are n (%) (cumulative event) unless otherwise indicated. The definitions of the primary composite endpoint and the thrombotic composite endpoint are as in Table 2.

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy.

FIGURE 5 Relative Risk Between Aspirin and Clopidogrel for Individual Outcomes

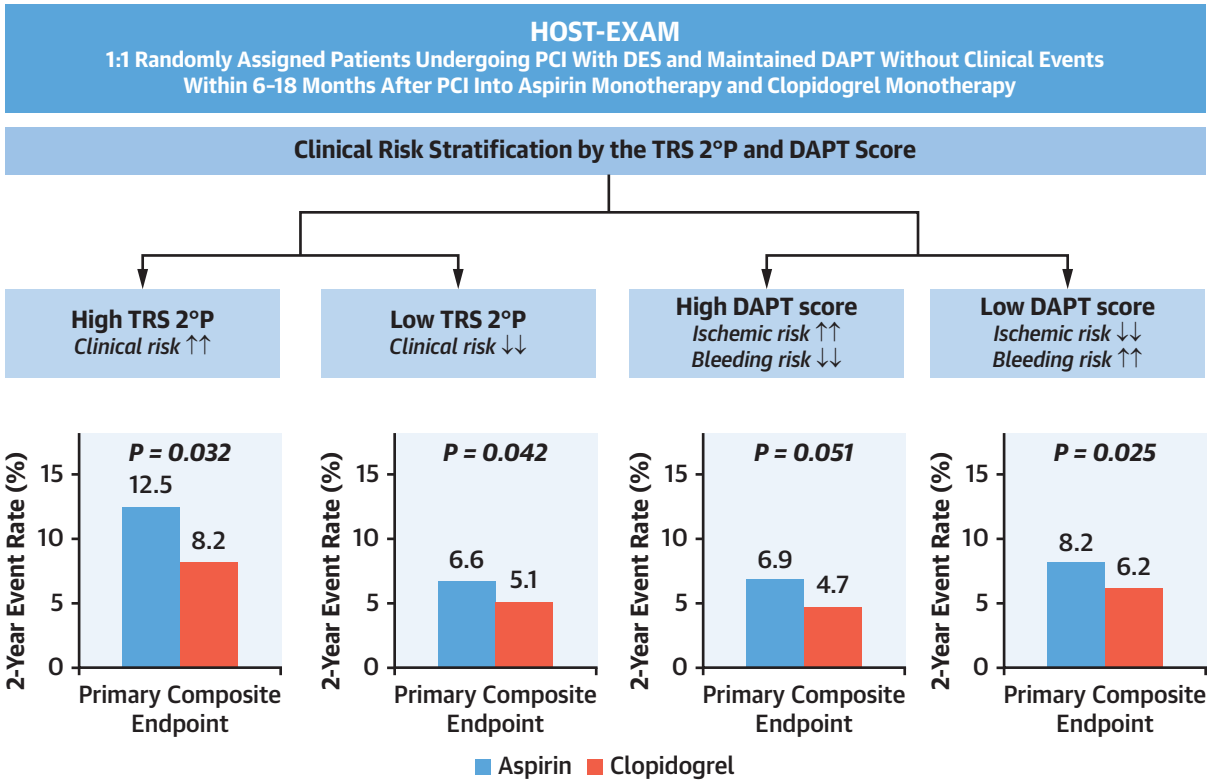


The relative risk between clopidogrel vs aspirin arms for the thrombotic composite endpoint and major bleeding events (Bleeding Academic Research Consortium type ≥3) in the high- and low-Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P) groups and in the high- and low-dual antiplatelet therapy (DAPT) score groups, estimated by a Bayesian analysis, is plotted. The definition of the thrombotic composite endpoint was as in Figure 1.

rate of MI increased, and the rate of major bleeding decreased with increasing DAPT score, suggesting that the DAPT score is a valid tool to uncouple ischemic and bleeding risks. This finding is in line with multiple studies that have validated the DAPT score in the wide population,[19-23] and our findings support the use of the DAPT score in assessment of the relative ischemic and bleeding risks.

Although aspirin has been used as the standard regimen for secondary prevention, a growing body of evidence has supported the better efficacy of $P2Y_{12}$ inhibitors over aspirin during the chronic phase after an acute vascular event.[24] The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial suggested that long-term administration of clopidogrel was associated with a lower risk of ischemic stroke, MI, or vascular death as compared with aspirin in patients with atherosclerotic vascular disease.[25] Recent systematic meta-analyses reported that $P2Y_{12}$ inhibitor monotherapy was associated with reduced risk for MI compared with aspirin monotherapy in the setting of secondary prevention.[26,27] Moreover, the HOST-EXAM trial demonstrated the superiority of clopidogrel monotherapy in preventing the composite of thrombotic and bleeding events in patients requiring indefinite antiplatelet monotherapy after PCI with DES.[3,4] On the other hand, integrative clinical risk assessment and the relative ischemic and bleeding risks should be incorporated into secondary prevention with antiplatelet therapy after PCI.[1,2] Our question was whether the benefits of clopidogrel observed in the HOST-EXAM trial hold up in patients according to the clinical, ischemic, and bleeding risk stratification. Therefore, we categorized patients

CENTRAL ILLUSTRATION **Outcomes After Aspirin vs Clopidogrel Monotherapy According to Clinical Risk**



Yang S, et al. J Am Coll Cardiol. 2023;82(16):1565–1578.

In this post hoc analysis of the HOST-EXAM trial, the high-TRS 2°P (≥3) group and the low-TRS 2°P group (<3) represented a high and low clinical risk, respectively. The high-DAPT score (≥2) group had an increased ischemic risk and a decreased bleeding risk, whereas the low-DAPT score (<2) group had an increased bleeding risk and a decreased ischemic risk. The beneficial effect of clopidogrel over aspirin was consistent across the high- and low-TRS 2°P groups and the high- and low-DAPT score groups. The definition of the primary endpoint is a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission because of acute coronary syndrome, and major bleeding events (Bleeding Academic Research Consortium type ≥3). DAPT = dual antiplatelet therapy; DES = drug-eluting stents; HOST-EXAM = Harmonizing Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy; PCI = percutaneous coronary intervention; TRS 2°P = Thrombolysis In Myocardial Infarction risk score for secondary prevention.

according to the TRS 2°P and the DAPT score and found that the benefit of clopidogrel over aspirin was consistent across high clinical, ischemic, and bleeding risks. To the best of our knowledge, this is the first report on the prognostic relevance of clopidogrel vs aspirin monotherapy, along with the integrative clinical risks and the relative ischemic and bleeding risks in terms of composite thrombotic and bleeding outcomes after PCI with DES. Our finding aligns with the post hoc analysis of the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial that additive risk reduction for adverse events of clopidogrel over aspirin was observed across the low-, intermediate-, and high-risk patients stratified by clinical risk score[28] and supports the use of clopidogrel monotherapy across various clinical risks and ischemic/bleeding risks. In the original HOST-EXAM study, the outcomes between the clopidogrel and aspirin groups started to diverge from 9 months after randomization, which has been observed in prior studies involving patients with no clinical events during DAPT maintenance.[3,4,29] A similar trend was observed across high and low DAPT score and TRS 2°P groups in the current study, where the gap between the clopidogrel and aspirin groups progressively widened after 9 months consistent with the HOST-EXAM study, which supports a continuous benefit of clopidogrel over aspirin regardless of clinical, ischemic, and bleeding risks.

In detail, we observed that clopidogrel could reduce both all bleeding and major bleeding in the high-TRS 2°P group or the low-DAPT score group that

was found to have a higher bleeding risk. Of note, among 9 hemorrhagic stroke events that occurred in the aspirin and high TRS 2°P group, 8 events were spontaneous bleeding except for 1 event caused by trauma, whereas there was no event in the clopidogrel and high TRS 2°P group. This finding reinforces a higher bleeding risk of aspirin vs clopidogrel in the high clinical risk group and is in line with previous studies that showed the amplified risk reduction for bleeding events by clopidogrel compared with aspirin in patients who had clinical risk factors such as recent ischemic stroke or ischemic events, cardiac surgery, or diabetes mellitus.[30-34] Moreover, our finding is in line with the prior study that clopidogrel use was associated with a lower risk of intracranial hemorrhage than aspirin use following primary acute ischemic stroke in patients aged ≥80 years,[35] or a network meta-analysis that showed the lowest risk of intracranial hemorrhage and major bleeding in clopidogrel users than aspirin, aspirin plus clopidogrel, and aspirin plus dipyridamole users in patients with noncardioembolic stroke.[36] Furthermore, the TWILIGHT-HBR (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention-High Bleeding Risk) study that reported a larger absolute risk reduction for bleeding events by early discontinuation of aspirin over prolonged DAPT in patients with high bleeding risk than those without high bleeding risk supports the current findings.[37] It is interesting to note that the significant benefit of clopidogrel for thrombotic events was also observed in the high DAPT score group that has a higher ischemic risk. This observation may be explained by the prior studies that $P2Y_{12}$ receptor inhibition was associated with a greater reduction of platelet function and thrombin formation than cyclooxygenase inhibition in moderate- to high-risk patients with coronary artery disease[38]; thereby, clopidogrel monotherapy can mitigate a prothrombotic state and prevent ischemic events in high clinical risk patients. Taken together, favorable clinical outcomes of clopidogrel over aspirin monotherapy can be expected in high clinical, ischemic, or bleeding risk patients.

STUDY LIMITATIONS. First, the open-labeled design of the study may cause a potential bias in outcomes reporting. Nonetheless, all clinical outcomes were validated and adjudicated by an independent committee blinded to randomization. Second, a post hoc analysis may have caused a type I error for comparing clinical events because the current study was not powered to compare outcomes according to the TRS 2°P or the DAPT score. Therefore, the results of the current analysis should be interpreted carefully and considered hypothesis-generating at best. Future studies are required to validate the current findings. Third, the current study was performed in the East Asian population, and the generalizability of the current results to other populations is limited. Fourth, there was a lack of information on the specific interventions and modifications for clinical risk factors during the follow-up period, and this might have influenced the event rate according to the TRS 2°P or DAPT score. However, all patients were recommended to receive up-to-date guideline-directed medical therapy. Fifth, phenotyping or genotyping, such as platelet function testing or testing for carriers of CYP2C19 loss-of-function alleles, was not done. Moreover, platelet reactivity on clopidogrel therapy can be affected by clinical risk factors, but the information on platelet reactivity was not available, which could be a potential confounder for the current analysis. Sixth, the number of events was small especially for bleeding events, which precludes any definitive conclusions on the benefit of clopidogrel for individual outcomes. Finally, the study population was stabilized PCI patients in whom the DAPT duration before study enrollment was wide at 6 to 18 months post-PCI. Therefore, our study cannot pinpoint the optimal duration of initial DAPT before antiplatelet monotherapy, nor can it be extrapolated to those who receive a shorter (<6 months) or longer (>18 months) duration of DAPT.

CONCLUSIONS

Compared with aspirin monotherapy, the benefit of clopidogrel in reducing the composite thrombotic and bleeding outcomes was consistent and maintained in patients with high and low clinical, ischemic, and bleeding risks.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Compared with aspirin monotherapy, clopidogrel reduced the risk of thrombotic events and major bleeding across a broad range of patient risk profiles.

TRANSLATIONAL OUTLOOK:

Additional studies are needed to compare the safety and efficacy of antiplatelet monotherapy with clopidogrel vs aspirin for secondary prevention of ischemic events in patients who have undergone PCI stratified by various clinical risk factors.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.

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