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DAPT Score and the Impact of Ticagrelor Monotherapy During the Second Year After PCI

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ABSTRACT

OBJECTIVES This study assessed the ability of the dual-antiplatelet therapy (DAPT) score in stratifying ischemic and bleeding risk in a contemporary percutaneous coronary intervention (PCI) population.

BACKGROUND The DAPT score is recommended by guidelines as a tool to stratify ischemic and bleeding risk. Its utility in contemporary PCI is unknown.

METHODS The study studied patients in GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation) who were free of major ischemic and bleeding events and adhered to antiplatelet strategy during the first year after PCI. The primary ischemic endpoint was the composite of myocardial infarction or stent thrombosis. The primary bleeding endpoint was Bleeding Academic Research Consortium type 3 or 5. Outcomes from 12 to 24 months after PCI were compared according to the DAPT score.

RESULTS Of 11,289 patients that were event-free after the first year, 6,882 and 4,407 patients had low (<2) and high (≥ 2) DAPT scores, respectively. Compared with a low DAPT score, patients with a high DAPT score had a higher rate of the composites of myocardial infarction or stent thrombosis (0.70% vs. 1.55%; $p < 0.0001$). The rate of Bleeding Academic Research Consortium type 3 or 5 bleeding was 0.54% and 0.30% in the low and high DAPT score groups, respectively ($p = 0.058$). The effect of ticagrelor versus aspirin monotherapy on primary ischemic and bleeding endpoints during the second year were no different among the 2 groups.

CONCLUSIONS The DAPT score can stratify ischemic but not bleeding risk in a contemporary PCI population during the second year. The score did not provide additional value for selection of antiplatelet strategy beyond the first year.
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The dual-antiplatelet therapy (DAPT) score was developed to predict both ischemic and bleeding risk and thereby help select patients who would benefit most from extended DAPT after the first year (1). Guidelines on DAPT have recognized the DAPT score as a tool to stratify ischemic and bleeding risk in patients treated with percutaneous coronary intervention (PCI) (2,3).

The DAPT score has been validated in several studies outside its derivation cohort; however, these studies have yielded conflicting results, in which some have confirmed its predictive value (4,5) and some have not (6,7). Of note, most of the analyses were from registries and substantial number of patients were treated with bare-metal stents or first-generation drug-eluting stents (DES). It is well known that using newer-generation DES mitigates the ischemic risk of patients treated with PCI (8). Hence, the performance of DAPT score in contemporary PCI practice has not been fully evaluated and needs further investigation.

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In GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation), 23-month ticagrelor monotherapy after 1-month DAPT (experimental strategy) was compared with aspirin monotherapy after 12-month DAPT (reference strategy) in all-comers patients treated with current PCI practice and newer-generation DES (9). In the second year after PCI, patients in the experimental arm received ticagrelor monotherapy while patients in the reference arm received aspirin monotherapy.

In the present analysis, we used the population of the GLOBAL LEADERS study to assess the ability of the DAPT score to stratify ischemic and bleeding risk in the second year after PCI. In addition, we assessed the effect of ticagrelor monotherapy versus aspirin monotherapy during the second year after PCI in patients stratified by the DAPT score.

METHODS

STUDY POPULATION. The GLOBAL LEADERS study (NCT01813435) was an investigator-initiated, prospective randomized, multicenter, open-label trial designed to evaluate 2 antiplatelet strategies after PCI using bivalirudin and biolimus A9 eluting stents in an all-comers population (9). In the first year after PCI, patients in the experimental arm were allocated to DAPT with aspirin 75 to 100 mg once daily in combination with ticagrelor 90 mg twice daily for 1 month followed by monotherapy with ticagrelor 90 mg twice daily until 1 year, while patients in the reference arm were allocated to DAPT with aspirin in combination with either ticagrelor (acute coronary

ABBREVIATIONS AND ACRONYMS

ARD = absolute risk difference

$ARD_{experimental-reference}$ = absolute risk difference for experimental minus reference strategy

BARC = Bleeding Academic Research Consortium

CI = confidence interval

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

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syndrome patients) or clopidogrel (stable coronary artery disease patients) for 12 months. In the second year, patients in the experimental arm continued ticagrelor monotherapy while patients in the reference arm stopped their $P2Y_{12}$ inhibitor and continued with aspirin monotherapy.

The GLOBAL LEADERS study was approved by the Institutional Review Board at each participating institution. All patients provided written informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice. An independent data and safety monitoring committee oversaw the safety of all patients.

The GLOBAL LEADERS study enrolled 15,991 patients between July 2013 to November 2015 in an "all-comers" design: no restriction regarding clinical presentation, complexity of the lesions, or number of stents used. Because 23 patients withdrew consent and requested data deletion from the database, a total of 15,968 patients remained in the main analysis.

To be included in the current analysis patients were required to: 1) have sufficient data to calculate their DAPT score; and 2) have completed the first year after the index PCI and be free of death, any stroke, myocardial infarction (MI), revascularization, definite or probable stent thrombosis (ST), and major bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5), together with adhering to their allocated antiplatelet strategy. Patients who had missing variables for calculation of the DAPT score were excluded from the analysis.

DAPT SCORE CALCULATION. The DAPT score was developed to simultaneously predict the ischemic and bleeding risk (1). The score ranges from -2 to 10 and consists of 9 variables including age, cigarette smoking, diabetes mellitus, MI at presentation, prior PCI or prior MI, paclitaxel-eluting stent, stent diameter <3 mm, congestive heart failure or left ventricular ejection fraction <30%, and vein graft stent (1). Patients were classified into 2 groups according to predetermined cutoff points of the DAPT score; a high score (DAPT score ≥2) indicated that the ischemic risk reduction from extended DAPT outweighed the risk of bleeding, whereas a low score (DAPT score <2) indicated that the increased risk of bleeding from extended DAPT outweighed the ischemic risk reduction.

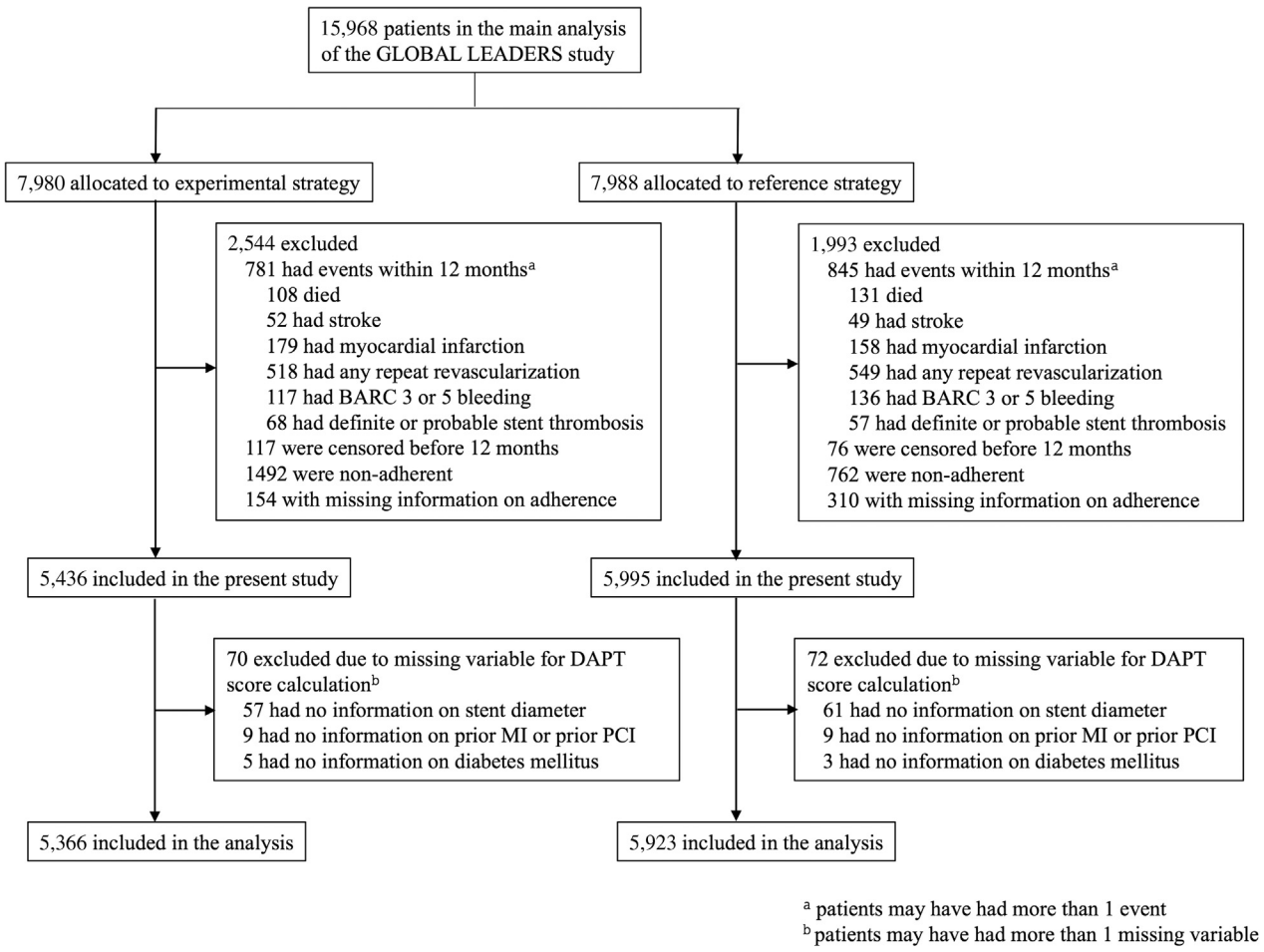
OUTCOMES. As in the DAPT study, the primary ischemic endpoint of the present study was a composite of MI or definite or probable ST. The ST was defined by the Academic Research Consortium definition (10). The primary bleeding endpoint was BARC type 3 or 5 (11) while in the DAPT study moderate to severe GUSTO (Global Use of Strategies to Open Coronary Arteries) bleeding was used (12). Additional endpoints were a composite of all-cause death, stroke or MI, and a composite of BARC type 2, 3, or 5 bleeding. Individual components of the composite endpoint were reported. The composite of all-cause death or new Q-wave MI, which was a primary endpoint of the main GLOBAL LEADERS study, and net adverse clinical events, which was defined as a composite of all-cause death, stroke, MI, or any revascularization, was also reported. Outcomes were analyzed in the study population from 12 months after index PCI until death, the first occurrence of the ischemic or bleeding events, loss to follow-up, or 24 months after the index PCI, which corresponds to the last follow-up visit in the GLOBAL LEADERS study.

STATISTICAL ANALYSIS. The DAPT score was calculated in study patients using the clinical information at the index PCI and the procedural information at the index and staged PCI. Study patients were stratified into 2 groups using the cutoff described in the DAPT score derivation study: high (≥2) or low (<2) DAPT score. Clinical and angiographic characteristics were compared between the 2 groups. Continuous variables are expressed as mean ± SD and were compared using independent Student's *t*-test. Categorical variables are presented as count and proportion and were compared using chi-square test. Outcomes were compared between the 2 groups. The Kaplan-Meier method was used to estimate the cumulative rates of events and the log-rank test was performed to examine the differences between the 2 groups. The association between each level of DAPT score and the risk of primary ischemic endpoint and primary bleeding endpoint were assessed using the spline function in the Cox regression analysis. Discrimination of ischemic and bleeding prediction models that were used to derive the DAPT score was assessed using Harrell's C-statistics (Online Appendix).

The impact of ticagrelor monotherapy versus aspirin monotherapy in the second year after PCI among the high and low DAPT score groups was assessed. We calculated the absolute risk difference (ARD), which was based on a difference in Kaplan-Meier estimate, and its 95% confidence interval (CI) between experimental and reference strategy among the DAPT score groups using the method described by Altman et al. (13), and were compared using the *Z*-test for interaction (14).

As a sensitivity analysis, we assessed the ability of the DAPT score to stratify ischemic and bleeding events during the second year in the reference and experimental groups separately because the DAPT score was originally developed in the cohort of patients

FIGURE 1 Flow Chart of the Study Population



The present study included patients in the GLOBAL LEADERS study who were free of major ischemic and bleeding events and adhered to their antiplatelet strategy during the first year after percutaneous coronary intervention (PCI). Adherence to the allocated antiplatelet strategies was assessed at discharge, 1-, 3-, 6-, and 12-month follow-up. Patients who were nonadherent at any time point during the first year after PCI and patients whom the information on adherence were missing were excluded from the present analysis. BARC = Bleeding Academic Research Consortium; DAPT = dual-antiplatelet therapy; MI = myocardial infarction.

who tolerated 12-month DAPT, and the duration of DAPT in the GLOBAL LEADERS study was different between the experimental and reference groups.

All analyses were performed on the intention-to-treat population. A 2-sided p value <0.05 was considered as statistically significant. All analyses were performed in R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 15,968 patients enrolled in the main analysis of the GLOBAL LEADERS study, 11,430 patients did not experience major ischemic and bleeding events and were adherent to their antiplatelet strategy in the first year after their index PCI (Figure 1). Of the 11,430 patients, the DAPT score was available in 11,289 (98.8%) patients, in which 6,882 patients had a low DAPT score and 4,407 patients had a high DAPT score (Online Figure 1). Apart from the differences in variables used for the DAPT score calculation, the group with a high DAPT score had a significantly higher proportion of patients with prior CABG, multivessel PCI, or more than 1 lesion treated, while the group with a low DAPT score had a significantly higher proportion of women and patients with hypertension, renal impairment, and left main PCI (Table 1).

ISCHEMIC AND BLEEDING RISK STRATIFICATION BY THE DAPT SCORE. The overall rate of MI or ST and BARC type 3 or 5 bleeding in the studied population

TABLE 1 Clinical and Angiographic Characteristics of Low and High DAPT Score Groups

	Low DAPT Score (n = 6,882)	High DAPT Score (n = 4,407)	p Value
Age, yrs	67.48 ± 9.65	58.56 ± 8.21	<0.0001
Body mass index, kg/m^2	27.95 ± 4.33	28.60 ± 4.85	<0.0001
Female	24.61 (1,694)	18.99 (837)	<0.0001
Diabetes mellitus	16.61 (1,143)	36.03 (1,588)	<0.0001
Insulin-treated	4.61 (317)	10.81 (474)	<0.0001
Hypertension	74.84 (5,136)	70.07 (3,076)	<0.0001
Hypercholesterolemia	70.03 (4,696)	70.18 (2,963)	0.8817
Current smoker	10.24 (705)	51.94 (2,289)	<0.0001
Peripheral vascular disease	5.49 (375)	5.91 (258)	0.3687
Chronic obstructive pulmonary disease	4.46 (306)	4.09 (179)	0.3687
Previous major bleeding	0.47 (32)	0.68 (30)	0.1664
Impaired renal function*	14.36 (983)	8.89 (390)	<0.0001
Prior stroke	2.37 (163)	2.27 (100)	0.7788
Previous myocardial infarction	16.45 (1,131)	31.21 (1,375)	<0.0001
Previous percutaneous coronary intervention	25.15 (1,731)	41.48 (1,828)	<0.0001
Previous coronary artery bypass grafting	4.64 (319)	6.06 (267)	0.001
Clinical presentation			<0.0001
Stable coronary artery disease	63.14 (4,345)	38.98 (1,718)	
Unstable angina	14.43 (993)	9.48 (418)	
Non-ST-segment elevation myocardial infarction	14.05 (967)	30.91 (1,362)	
ST-segment elevation myocardial infarction	8.38 (577)	20.63 (909)	
Heart failure or left ventricular ejection fraction <30%	0.65 (45)	6.40 (282)	<0.0001
Lesions treated	1.36 ± 0.69	1.49 ± 0.78	<0.0001
Lesions treated per patient			<0.0001
1	72.92 (5,008)	64.70 (2,846)	
2	20.21 (1,388)	24.82 (1,092)	
3 or more	6.87 (472)	10.48 (461)	
Left main PCI	2.68 (184)	2.09 (92)	0.0566
Right coronary artery PCI	36.23 (2,488)	38.01 (1,672)	0.0584
Left anterior descending artery PCI	53.57 (3,679)	47.65 (2,096)	<0.0001
Left circumflex artery PCI	27.23 (1,870)	38.03 (1,673)	<0.0001
Saphenous vein graft PCI	0.25 (17)	2.09 (92)	<0.0001
Number of stent per patient	1.62 ± 0.99	1.81 ± 1.10	<0.0001
Multivessel PCI	19.57 (1,344)	25.05 (1,102)	<0.0001
Bifurcation PCI	15.01 (1,031)	15.98 (703)	0.1725
Mean stent length, mm	24.18 ± 12.46	25.50 ± 13.04	<0.0001
Stent diameter <3 mm	38.45 (2,646)	65.49 (2,886)	<0.0001

Values are mean ± SD or % (n). *Defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 based on the Modification of Diet in Renal Disease formula.
DAPT = dual-antiplatelet therapy; PCI = percutaneous coronary intervention.

were 1.03% and 0.44%, respectively. Compared with the low DAPT score group, patients with a high DAPT score had a higher rate of the composite of MI or ST (1.55% vs. 0.70%; p < 0.0001) and all-cause death, stroke, or MI (2.31% vs. 1.98%; p = 0.0037) (**Figure 2**).

The rate of BARC type 3 or 5 bleeding was 0.54% and 0.30% in the low and high DAPT score groups, respectively (p = 0.058). The rate of BARC type 2, 3, or 5 bleeding was 1.66% in the low DAPT score group, whereas it was 1.21% in the high DAPT score group (p = 0.0574).

There were no between-group differences in the rates of all-cause mortality and any stroke (**Table 2**). In the sensitivity analysis, the ability of the DAPT score to stratifying ischemic and bleeding risk was not different between patients in the experimental and reference group and may not be affected by the duration of DAPT during the first year (Online Table 1).

The C-statistic of the ischemic prediction model of the DAPT score for MI or ST was 0.64 (95% CI: 0.59 to 0.70), while the C-statistic of the bleeding prediction

TABLE 2 Outcomes From 12 to 24 Months According to DAPT Score Group

	Overall	Low DAPT Score	High DAPT Score	Log-Rank p Value
MI or definite/probable stent thrombosis	1.03 (116)	0.70 (48)	1.55 (68)	<0.0001
MI	0.96 (108)	0.66 (45)	1.44 (63)	<0.0001
Definite or probable stent thrombosis	0.23 (26)	0.15 (10)	0.37 (16)	0.0186
All-cause death/stroke/MI	2.31 (260)	1.98 (136)	2.82 (124)	0.0037
All-cause death or new Q-wave MI	1.51 (169)	1.48 (101)	1.55 (68)	0.7576
All-cause death	1.09 (123)	1.06 (73)	1.14 (50)	0.7146
New Q-wave MI	0.45 (50)	0.48 (32)	0.42 (18)	0.6537
Stroke	0.40 (45)	0.41 (28)	0.39 (17)	0.8619
BARC type 3 or 5 bleeding	0.44 (50)	0.54 (37)	0.30 (13)	0.0580
BARC type 2, 3, or 5 bleeding	1.48 (162)	1.66 (110)	1.21 (52)	0.0574
BARC type 5 bleeding	0.10 (11)	0.07 (5)	0.14 (6)	0.2925
BARC type 3 bleeding	0.40 (45)	0.50 (34)	0.25 (11)	0.0442
BARC type 2 bleeding	1.10 (120)	1.18 (78)	0.98 (42)	0.3273
Net clinical adverse events	4.96 (559)	4.66 (320)	5.43 (239)	0.063

Values shown are Kaplan-Meier estimates in % (n).
BARC = Bleeding Academic Research Consortium; MI = myocardial infarction.

model of the DAPT score for BARC type 3 or 5 bleeding was 0.69 (95% CI: 0.62 to 0.76). The C-statistics were similar to or higher than in the original validation cohort of the DAPT score (Online Table 2).

The risk of MI or ST gradually rises as the DAPT score increases (**Central Illustration**). In contrast, the DAPT score had a U-shaped association with the risk of BARC type 3 or 5 bleeding.

ANTIPLATELET STRATEGY IN THE SECOND YEAR AFTER PCI AND DAPT SCORE. At the end of the second year after PCI, compared with the reference strategy, the experimental strategy was associated with a lower rate of MI or ST (0.82% vs. 1.22%; log-rank p = 0.0376; ARD for experimental minus reference strategy [$ARD_{experimental\text{-}reference}$] -0.40; 95% CI: -0.77% to -0.03%) and the composite of all-cause mortality, stroke, or MI (1.92% vs. 2.65%; log-rank p = 0.0100; $ARD_{experimental\text{-}reference}$ -0.73%; 95% CI: -1.28% to -0.18%) (**Figure 3**, Online Table 3). The rate of BARC type 3 or 5 bleeding was not different between the 2 antiplatelet strategies (0.54% vs. 0.36%; log-rank p = 0.1381; $ARD_{experimental\text{-}reference}$ 0.19%; 95% CI: -0.06% to 0.44%), whereas the rate of BARC type 2, 3 or 5 bleeding was higher in the experimental strategy versus the reference strategy (1.80% vs. 1.19%; log-rank p = 0.0080; $ARD_{experimental\text{-}reference}$ 0.61%; 95% CI: 0.16 to 1.07).

The event rates at the end of the second year after PCI, according to antiplatelet strategies and DAPT score group, are shown in **Table 3**. In both the low and high DAPT score groups, the experimental strategy was associated with a reduction of MI or ST ($ARD_{experimental\text{-}reference}$: low DAPT score -0.51%; 95% CI: -0.89% to -0.12%; high DAPT score -0.25%; 95% CI: -0.98% to 0.48%; $p_{interaction}$ = 0.5425) (**Figure 4**). The finding was similar when the composite endpoint of all-cause mortality, stroke, or MI was tested as an ischemic event ($ARD_{experimental\text{-}reference}$: low DAPT score -0.88%; 95% CI: -1.53% to -0.23%; high DAPT score -0.51%; 95% CI: -1.49% to 0.46%; $p_{interaction}$ = 0.5362).

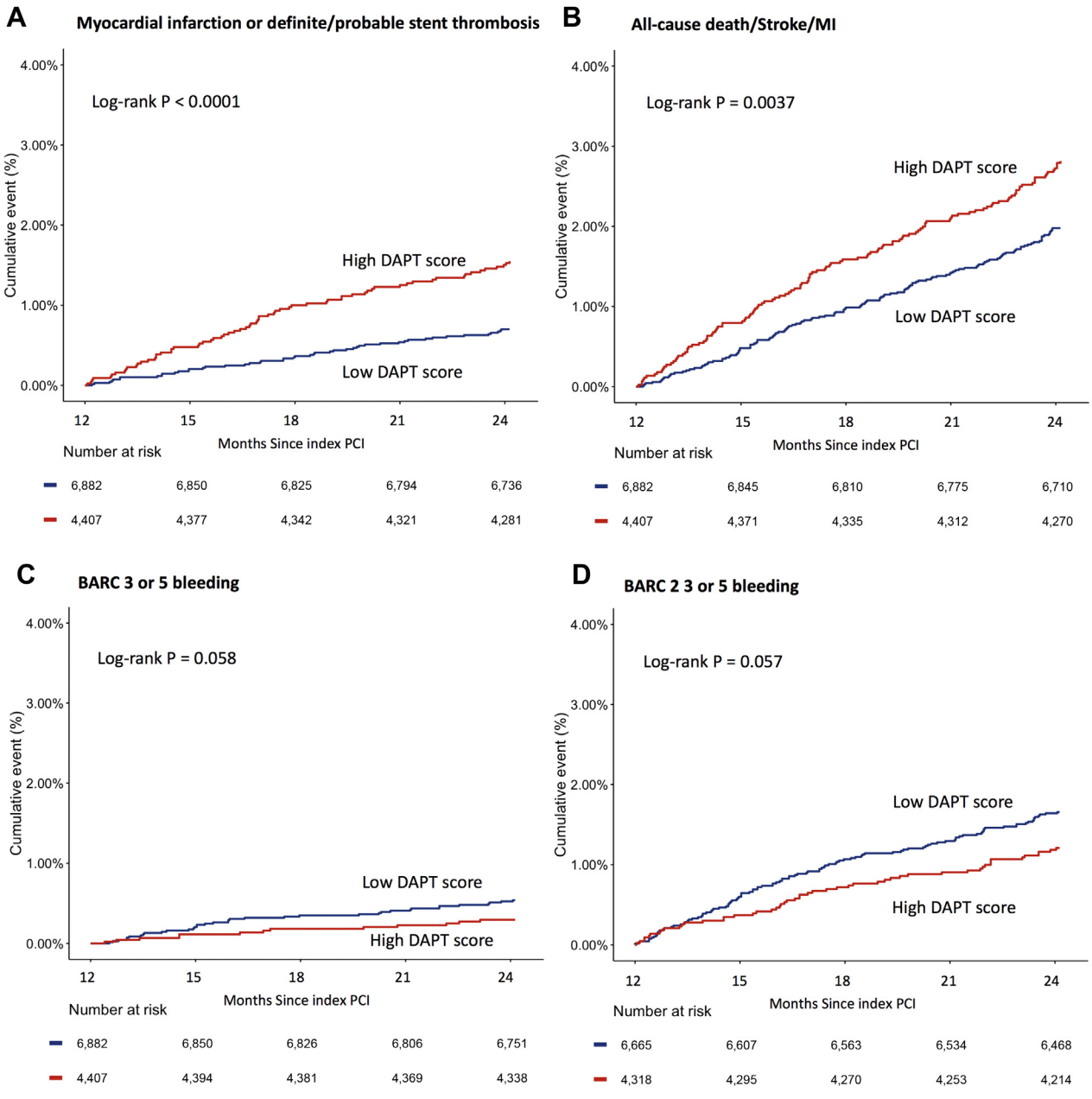
Compared with the reference strategy, the experimental strategy was not associated with a significantly higher rate of BARC type 3 or 5 bleeding in both low and high DAPT score groups ($ARD_{experimental\text{-}reference}$: low DAPT score 0.32%; 95% CI: -0.03% to 0.68%; high DAPT score -0.02%; 95% CI: -0.34% to 0.30%; $p_{interaction}$ = 0.1535). The experimental strategy was associated with an excess of BARC type 2, 3, or 5 bleeding regardless of DAPT score group ($ARD_{experimental\text{-}reference}$: low DAPT score 0.66%; 95% CI: 0.04% to 1.28%; high DAPT score 0.55%; 95% CI: -0.11% to 1.21%; $p_{interaction}$ = 0.8181) (**Figure 4**).

The event rates at the end of the second year after PCI according to each level of the DAPT score and the assigned antiplatelet strategy are shown in the Online Table 4.

DISCUSSION

The main findings of the present study are the following: 1) patients with a high DAPT score had higher rate of MI or ST than did those with a low DAPT score; 2) patients with a low DAPT score had a higher rate of BARC type 3 or 5 bleeding than did patients with a high DAPT score; however, the difference was

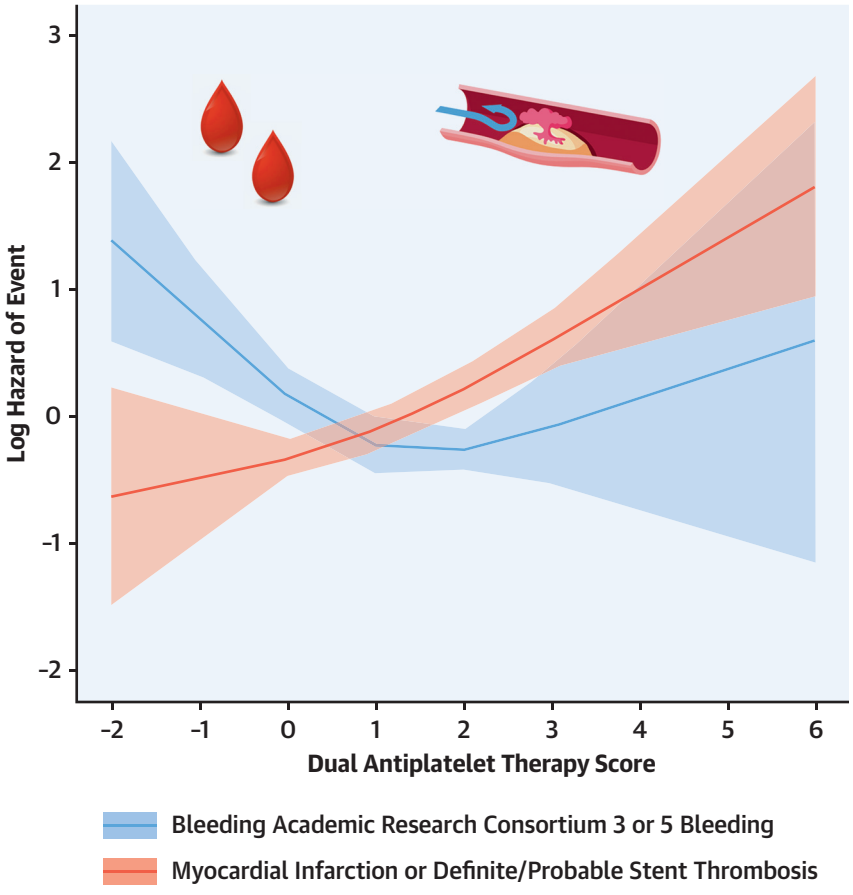
FIGURE 2 **Ischemic and Bleeding Outcomes From 12 to 24 Months After PCI According to DAPT Score Group**



Time-to-first event curves for the ischemic and bleeding outcomes from 12 to 24 months after PCI in the study population with low **(blue line)** and high **(red line)** DAPT score. **(A)** MI or definite or probable stent thrombosis; **(B)** composite of all-cause death, stroke, or MI; **(C)** BARC type 3 or 5 bleeding; and **(D)** BARC type 2, 3 or 5 bleeding. Abbreviations as in Figure 1.

not statistically significant; 3) in patients who were free of the major events and were adherent to the antiplatelet therapy during the first year after PCI, as in the DAPT study, treatment with ticagrelor monotherapy during the second year was associated with a lower rate of MI or ST and a similar rate of BARC type 3 or 5 bleeding to aspirin monotherapy; and 4) the effect of antiplatelet strategy on MI or ST and bleeding during the second year after the index PCI was not different among the low and high DAPT score groups, as shown by a negative p value for interaction.

CENTRAL ILLUSTRATION **Association Between the DAPT Score and the Ischemic or Bleeding Risk**



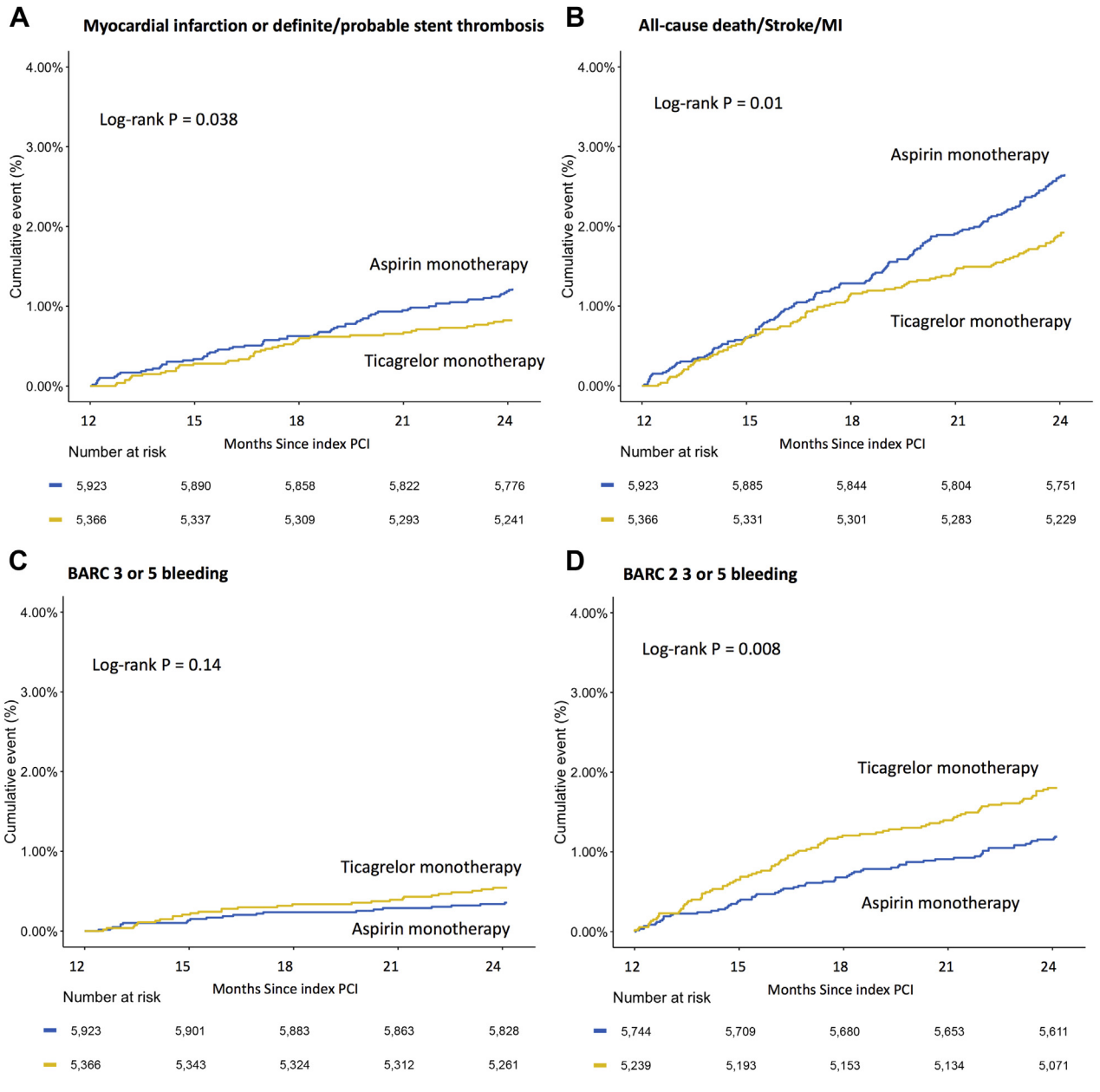
Chichareon, P. et al. J Am Coll Cardiol Intv. 2020;13(5):634–46.

Smooth spline curves of the association between DAPT score and the risk of myocardial infarction or stent thrombosis **(red line)** and BARC 3 or 5 bleeding **(blue line)**. **Shading** represents the area of 95% confidence interval.

RISK STRATIFICATION OF ISCHEMIA AND BLEEDING BY DAPT SCORE. The focused update on DAPT in coronary artery disease by the European Society of Cardiology has recognized the DAPT score as a tool for stratifying ischemia and bleeding risk. However, the European Society of Cardiology guidelines have also called for additional validation in less well-selected populations, treated only with new-generation DES (3).

The DAPT score has been tested in several different populations with conflicting results. It effectively stratified the ischemic and bleeding risk in a pooled cohort of 3 studies enrolling Japanese patients treated with DES (5) and in the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) all-comers registry (4). Conversely, it failed to differentiate the ischemic and bleeding events in the patients enrolled in the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial (6). Recently Ueda et al. (7) validated the score in a large Swedish registry, concluding that it did not adequately stratify bleeding risks, while its discrimination of ischemic risk was poor. The findings from this study led to questions about the score's application in a real-world population. Nevertheless, there are some limitations to these studies which need to be acknowledged (15). First, it may not be appropriate to evaluate the DAPT score using the C-statistics for individual outcomes because the C-statistic is a unified score integrating both ischemic and bleeding risks,

FIGURE 3 **Ischemic and Bleeding Outcomes From 12 to 24 Months After PCI According to Antiplatelet Strategies**



Time-to-first event curves for the ischemic and bleeding outcomes from 12 to 24 months after PCI in the patients with ticagrelor monotherapy **(yellow line)** and aspirin monotherapy **(blue line)**. **(A)** MI or definite or probable stent thrombosis; **(B)** composite of all-cause death, stroke, or MI; **(C)** BARC type 3 or 5 bleeding; and **(D)** BARC type 2, 3, or 5 bleeding. Abbreviations as in Figure 1.

and its main purpose is to uncouple ischemia from bleeding risk (15). Second, most of the validation cohorts dated from the period when the new-generation DES and potent $P2Y_{12}$ inhibitor were not widely used.

In the present analysis, by using the DAPT score, we could identify patients with a high DAPT score who had a 2-fold higher rate of MI or ST than did patients with a low DAPT score. However, the score could not identify groups of patients with significant difference in the risk of bleeding during the second year after PCI. The relatively low rate of bleeding during the second year after PCI in the present study

TABLE 3 Outcomes From 12 to 24 Months by Antiplatelet Strategy According to DAPT Score Group

	Low DAPT Score (DAPT Score <2) (n = 6,882)				High DAPT Score (DAPT Score ≥2) (n = 4,407)				
	Experimental Strategy	Reference Strategy	p Value	ARD* (95% CI)	Experimental Strategy	Reference Strategy	p Value	ARD* (95% CI)	p for Interaction
MI or definite/probable stent thrombosis	0.43 (14)	0.94 (34)	0.0122	-0.51 (-0.89 to -0.12)	1.42 (30)	1.67 (38)	0.5089	-0.25 (-0.98 to 0.48)	0.5425
MI	0.37 (12)	0.91 (33)	0.0057	-0.54 (-0.91 to -0.17)	1.18 (25)	1.67 (38)	0.179	-0.49 (-1.19 to 0.21)	0.8945
Definite or probable stent thrombosis	0.06 (2)	0.22 (8)	0.0852	-0.16 (-0.34 to 0.01)	0.38 (8)	0.35 (8)	0.8786	0.03 (-0.33 to 0.38)	0.3571
All-cause death/stroke/MI	1.51 (49)	2.39 (87)	0.0087	-0.88 (-1.53 to -0.23)	2.55 (54)	3.06 (70)	0.3068	-0.51 (-1.49 to 0.46)	0.5362
All-cause death or new Q-wave MI	1.34 (43)	1.61 (58)	0.3413	-0.27 (-0.85 to 0.30)	1.52 (32)	1.58 (36)	0.8587	-0.07 (-0.80 to 0.67)	0.6606
All-cause death	0.83 (27)	1.27 (46)	0.0799	-0.43 (-0.91 to 0.04)	1.13 (24)	1.14 (26)	0.9888	0.00 (-0.63 to 0.62)	0.2843
New Q-wave MI	0.54 (17)	0.42 (15)	0.5059	0.12 (-0.22 to 0.45)	0.38 (8)	0.44 (10)	0.7538	-0.06 (-0.44 to 0.32)	0.4947
Stroke	0.37 (12)	0.44 (16)	0.6466	-0.07 (-0.37 to 0.23)	0.33 (7)	0.44 (10)	0.5679	-0.11 (-0.47 to 0.26)	0.8769
BARC type 3 or 5 bleeding	0.71 (23)	0.39 (14)	0.0672	0.32 (-0.03 to 0.68)	0.28 (6)	0.31 (7)	0.8867	-0.02 (-0.34 to 0.30)	0.1535
BARC type 2, 3, or 5 bleeding	2.00 (63)	1.35 (47)	0.0352	0.66 (0.04 to 1.28)	1.49 (31)	0.94 (21)	0.099	0.55 (-0.11 to 1.21)	0.8181
BARC type 5 bleeding	0.03 (1)	0.11 (4)	0.2236	-0.08 (-0.20 to 0.03)	0.19 (4)	0.09 (2)	0.3631	0.10 (-0.10 to 0.32)	0.1446
BARC type 3 bleeding	0.68 (22)	0.33 (12)	0.0402	0.35 (0.01 to 0.69)	0.19 (4)	0.31 (7)	0.435	-0.12 (-0.41 to 0.18)	0.0414
BARC type 2 bleeding	1.34 (42)	1.03 (36)	0.2456	0.30 (-0.22 to 0.83)	1.25 (26)	0.72 (16)	0.0747	0.54 (-0.06 to 1.13)	0.5678
Net clinical adverse events	4.01 (130)	5.23 (190)	0.0166	-1.22 (-2.21 to -0.23)	5.19 (110)	5.64 (129)	0.5161	-0.45 (-1.79 to 0.89)	0.3653

Values are Kaplan-Meier estimates in % (n) unless otherwise indicated. *ARD between experimental and reference strategy—a negative value represents absolute reduction of event with experimental strategy while a positive value represents absolute increase of event with experimental strategy.

ARD = absolute risk difference; CI = confidence interval; other abbreviations as in Tables 1 and 2.

could be one of the explanations why the DAPT score could not differentiate the risk of bleeding between the 2 groups. In addition, the incidence of post-PCI bleeding in the first year after PCI is usually higher than in the second year or after (16). Therefore, these findings emphasize the importance of early ischemic and bleeding risk stratification and the need for decision making with risk scores to select antiplatelet strategies during the early period after PCI in individual patients undergoing contemporary PCI.

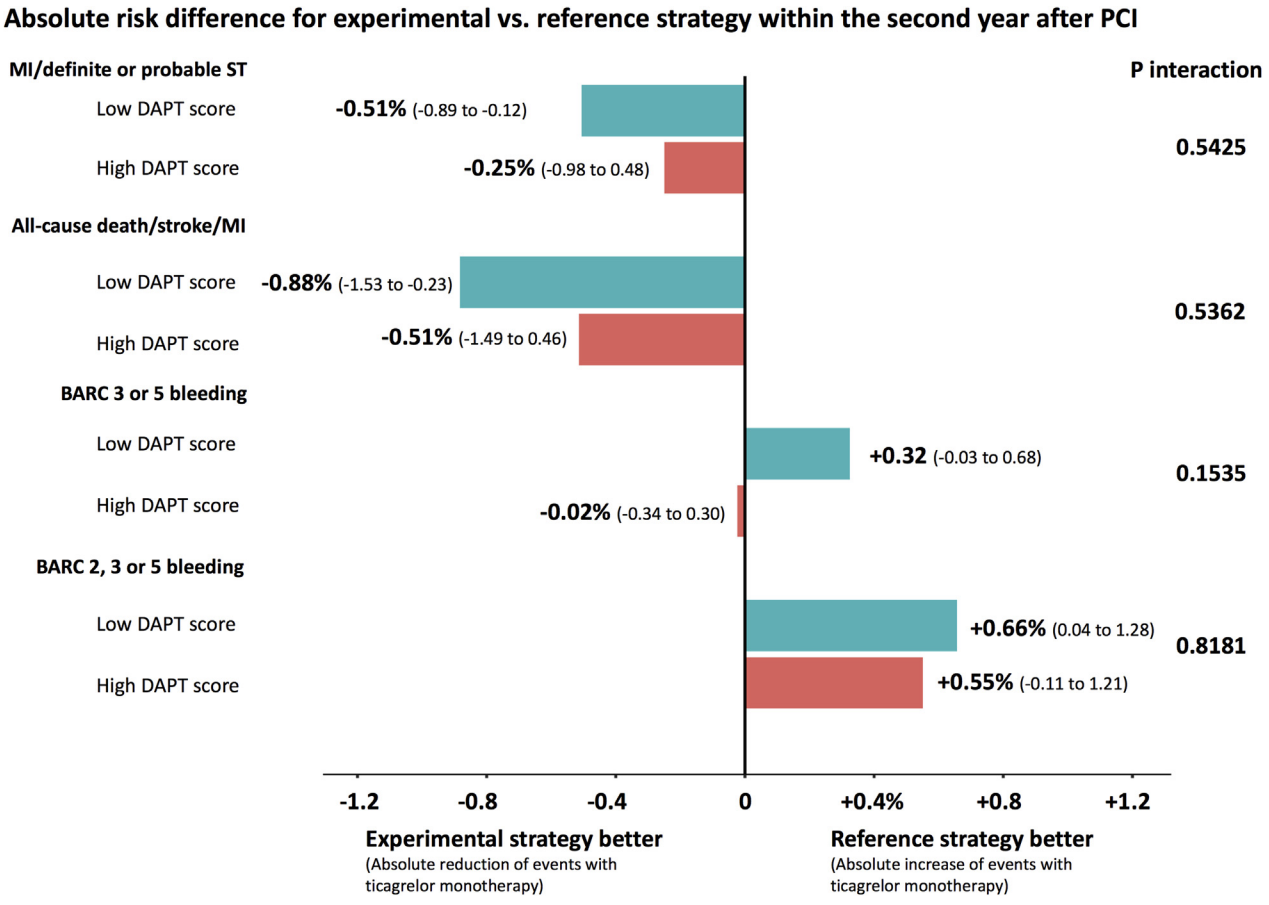
The exploratory analysis using a DAPT score cutoff of 1 was performed because the distribution of the DAPT score in the present study was different from that in the DAPT study (Online Figure 2) including paclitaxel-eluting stents, which contributed substantially to the parameter of the DAPT score, and is no longer used in the current practice. The cutoff of 1 may be better in differentiating the ischemic and bleeding risk; however, this analysis is absolutely exploratory and further studies are warranted (Online Tables 5 and 6).

ANTIPLATELET STRATEGY BEYOND THE FIRST YEAR AND DAPT SCORE. The DAPT study showed that, in patients who were free from the major ischemic and bleeding event in the first year after DES implantation and were adherent to antiplatelet therapy, the extension of DAPT beyond 1 year was superior to aspirin monotherapy in reducing the risk of ST and major adverse cardiovascular and cerebrovascular events (12), however, this extension increased the risk of bleeding. The design of the GLOBAL LEADERS study was different from the DAPT study; however, the experimental strategy was based on the same principle that long-term intense platelet inhibition may offer a protective effect against ischemic events, in a similar fashion as in the extended DAPT, without substantial increase in the risk of bleeding.

The concept of using $P2Y_{12}$ inhibitor monotherapy, instead of aspirin, to prevent ischemic events in patients with atherosclerotic cardiovascular disease is not new and dates back to decades ago. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event) study showed that clopidogrel was superior to aspirin monotherapy in reducing the rate of the composite ischemic endpoint and was not associated with increased bleeding risk (17). A single-center study supported results of the CAPRIE study in which clopidogrel monotherapy during the second year after DES implantation was associated with a reduction in ischemic events compared with aspirin monotherapy, while the bleeding risk was similar (18). However, the study was inherently limited by its retrospective nature and the results from dedicative randomized controlled trials in patients treated with DES are needed.

The efficacy and safety of potent $P2Y_{12}$ inhibitor monotherapy during the first year after PCI was tested in the TWILIGHT (Ticagrelor With Aspirin or

FIGURE 4 DAPT Score and Antiplatelet Strategy During the Second Year After PCI



Absolute risk difference between the experimental strategy (ticagrelor monotherapy) vs. the reference strategy (aspirin monotherapy) on the outcomes during the second year after PCI among DAPT score group: a negative value represents absolute reduction of event with experimental strategy whereas a positive value represents absolute increase of event with experimental strategy. Abbreviations as in Figure 1.

Alone in High-Risk Patients After Coronary Intervention) study (19). Ticagrelor monotherapy significantly reduced the risk of bleeding, while it was noninferior to ticagrelor plus aspirin in terms of ischemic risk. To date, the benefit of potent $P2Y_{12}$ inhibitor monotherapy beyond the first year after PCI has not been established in the dedicated randomized controlled trial. In the present exploratory analysis, we have demonstrated that ticagrelor monotherapy during the second year was associated with a lower rate of MI or ST compared with aspirin monotherapy in the patients who fulfilled the inclusion criteria of the DAPT study. The rate of clinically relevant bleeding (BARC type 2, 3, or 5 bleeding) in the group allocated to ticagrelor monotherapy was higher than that in the group of aspirin monotherapy; however, the rate of major bleeding (BARC type 3 or 5 bleeding) was similar between the 2 groups. This finding is supported by the in vitro study showing that aspirin offers small effect on platelet inhibition in the presence of potent $P2Y_{12}$ inhibitor, and clinically, adding aspirin to the potent $P2Y_{12}$ inhibitor may not provide additional ischemic protection but may increase the risk of bleeding in patients (20).

The effect of ticagrelor monotherapy versus aspirin monotherapy was not different among the low and high DAPT score groups, as indicated by a negative interaction test. Inevitably, this analysis was a post hoc exploration and may suffer from inadequate power to detect a difference. Nevertheless, the concept of long-term platelet inhibition with potent antiplatelet regimens in selected patients after PCI who had ischemic risk outweighs bleeding risk warrants further investigation.

STUDY LIMITATIONS. First, the present study is a post hoc analysis in a selected population in the GLOBAL LEADERS study. Therefore, the results should be interpreted with caution and considered as hypothesis-generating. Second, in the present study, DAPT score was calculated using clinical information at the index PCI; hence, some variables such as cigarette smoking or diabetic status could have changed or developed during the first year after PCI. Third, the event rates in the present study, even after adjusting for the different period of follow-up, were relatively low compared with those in the DAPT study. Hence, the results were at risk for type II error to demonstrate significant differences between 2 comparisons. Fourth, the difference in the bleeding definition between the DAPT study (GUSTO definition) and the GLOBAL LEADERS study (BARC definition) may affect the assessment of the DAPT score performance. However, the rates of moderate or severe GUSTO bleeding and the BARC type 3 and 5 bleeding were comparable in the DAPT study (12). Fifth, because the DAPT regimens in the first year were different between the experimental and reference strategy, the number of patients who were excluded because of the events during the first year was different between the 2 groups. This difference caused some imbalance in patient characteristics between the 2 groups and might influence the results on the effect of antiplatelet strategies between the 2 DAPT score groups (Online Tables 7 to 9).

Finally, there was no central and global adjudication for serious adverse events in this investigator-driven trial, and the endpoints were site-reported. Nevertheless, there was regular monitoring and on-site visits for consistency of event definitions and underreport of the events.

CONCLUSIONS

The DAPT score can stratify ischemic but not bleeding risk during the second year in the GLOBAL LEADERS study population. The effect of antiplatelet strategy during the second year after PCI was not different among the low and high DAPT score groups. The value of the score to select the optimal antiplatelet regimen during the second year after PCI warrants further investigation.

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PERSPECTIVES

WHAT IS KNOWN? The DAPT score is recommended by guidelines as a tool to stratify ischemic and bleeding risk beyond the first year after PCI, and the score may identify patients who would benefit from long-term potent $P2Y_{12}$ inhibitor.

WHAT IS NEW? The DAPT score can stratify ischemic but not bleeding risk beyond the first year after contemporary PCI. Compared with aspirin monotherapy, ticagrelor monotherapy during the second year after PCI may be associated with a reduction in the risk of ischemic events without an increase in the risk of major bleeding.

WHAT IS NEXT? The concept of long-term platelet inhibition with potent antiplatelet regimens in selected patients after PCI who had ischemic risk outweighs bleeding risk warrants further investigation.

REFERENCES

1. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention: an analysis from the randomized Dual Antiplatelet Therapy study. JAMA 2016;315:1735–49.

2. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

3. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–60.

4. Brener SJ, Kirtane AJ, Rinaldi MJ, et al. Prediction of ischemic and bleeding events using the dual antiplatelet therapy score in an unrestricted percutaneous coronary intervention population. Circulation: Cardiovascular Interventions 2018;11:e006853.

5. Yoshikawa Y, Shiomi H, Watanabe H, et al. Validating utility of dual antiplatelet therapy score in a large pooled cohort from 3 Japanese percutaneous coronary intervention studies. Circulation 2018;137:551–62.

6. Harada Y, Michel J, Lohaus R, et al. Validation of the DAPT score in patients randomized to 6 or 12 months clopidogrel after predominantly second-generation drug-eluting stents. Thromb Haemost 2017;117:1989–99.

7. Ueda P, Jernberg T, James S, et al. External validation of the DAPT score in a nationwide population. J Am Coll Cardiol 2018;72:1069–78.

8. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, non-inferiority trial. J Am Coll Cardiol Intv 2013;6:777–89.

9. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor

monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940–9.

10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

12. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

13. Altman D, Machin D, Bryant T. Statistics with Confidence: Confidence Intervals and Statistical Guidelines. London, United Kingdom: Wiley, 2000.

14. Altman DG, Bland JM. Interaction revisited: the difference between 2 estimates. BMJ 2003;326:219.

15. Yeh RW, Kereiakes DJ, Secemsky EA, Steg PG, Mauri L. The DAPT score in Sweden: successful validation, flawed interpretation. J Am Coll Cardiol 2019;73:113–4.

16. Valle JA, Shetterly S, Maddox TM, et al. Postdischarge bleeding after percutaneous coronary intervention and subsequent mortality and myocardial infarction: insights from the HMO Research Network-Stent Registry. Circ Cardiovas Interv 2016;9:e003519.

17. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39.

18. Park TK, Song YB, Ahn J, et al. Clopidogrel versus aspirin as an antiplatelet monotherapy after 12-month dual-antiplatelet therapy in the era of drug-eluting stents. Circ Cardiovasc Interv 2016;9:e002816.

19. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–42.

20. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15:480–96.

KEY WORDS bleeding, dual-antiplatelet therapy score, myocardial infarction, percutaneous coronary intervention, risk stratification, ticagrelor

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