Risk/Benefit Tradeoff of Prolonging Dual Antiplatelet Therapy More Than 12 Months in TWILIGHT-Like High-Risk Patients After Complex Percutaneous Coronary Intervention

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Patients who underwent complex percutaneous coronary intervention (PCI) are known to be at high risk for both ischemic and bleeding complications. The risk/benefit tradeoff of extending dual antiplatelet therapy (DAPT) >12 months with clopidogrel and aspirin for TWILIGHT-like patients who are at high risk of bleeding or ischemic events and undergo complex PCI is unclear. Eight thousand three hundred and fifty-eight consecutive patients fulfilling the "TWILIGHT-like" criteria who underwent PCI from January 2013 to December 2013 were prospectively enrolled in Fuwai PCI Registry. We identified 2,677 of "TWILIGHT-like" complex PCI patients who were events free at 1 year after the index procedure. "TWILIGHT-like" patients were identified based on at least 1 clinical and 1 angiographic feature. Median follow-up was 29 months. Risk of primary efficacy outcome, major adverse cardiac and cerebrovascular events (composite of all-cause death, myocardial infarction, or stroke), was reduced with DAPT >12 months versus DAPT≤ 12 months (hazard ratio $[HR]_{adj}$ 0.374, 95% confidence interval [CI] 0.235 to 0.595; $HR_{matched}$ 0.292 [0.151 to 0.561]; HR_{IPTW} 0.356 [0.225 to 0.562]), with directional consistency for cardiovascular death and definite/probable stent thrombosis. In contrast, >12-month DAPT was comparable to ≤12-month DAPT for the risk of clinically relevant bleeding ($[HR]_{adj}$ 1.189, 95% CI 0.474 to 2.984; $HR_{matched}$ 1.577 [0.577 to 4.312]; HR_{IPTW} 1.239 [0.502 to 3.059]). Importantly, there was also a significant net benefit in favor of prolonged DAPT treatment. In conclusion, among "TWILIGHT-like" patients after complex PCI, continuing duration of DAPT> 12 months was associated with a net clinical benefit and lower rates of ischemic events without increasing the risk of clinically relevant bleeding than DAPT≤ 12 months, suggesting that long-term DAPT may have a favorable risk-benefit ratio in this high-risk population. **(Am J Cardiol 2020;133:61−70)**

The current data remain inconclusive with regard to optimal potency and duration of dual antiplatelet therapy (DAPT).[1,2] The ideal approach should be balancing the estimated risks of recurrent ischemic and bleeding events based on evaluation of patient's clinical and procedural factors. Against this background, the TWILIGHT trial used a set of clinical (e.g., diabetes mellitus) and angiographic (e.g., multivessel disease) enrichment criteria to identify patients who are at high risk of either thrombotic or hemorrhagic complications postpercutaneous coronary intervention (PCI).[3,4] At present, most PCI with drug-eluting stent (DES) are increasingly performed in complex clinical and anatomical subsets of patients.[5−7] It was worthy of noting that complex PCI is an important parameter associated with a higher risk for ischemic events,[7−10] and justifies, at least in part, the potential benefit offered by extended DAPT regimen in this patient category.[8,9] On the other hand, complex PCI criteria were also associated with a higher bleeding risk[10,11] and patients who underwent complex PCI simultaneously carry characterizes that significantly increase their bleeding hazards, such as advanced age, renal impairment, and higher burden of comorbidities.[12,13] Given the risk after complex PCI might further compounded in the setting of high-risk "TWILIGHT-like" patients who are at high risk of ischemic or bleeding events, implementation of antiplatelet strategies associated with a favorable benefit-risk ratio in this patient population is of paramount importance.

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In this regard, we sought to evaluate the benefit/risk trade-off of DAPT beyond 12 months as compared with ≤12-month DAPT in high-risk "TWILIGHT-like" patients who underwent complex PCI with DES, using data from a large prospective, observational, single-center registry.

Methods

Ten thousand one hundred and sixty-seven consecutive patients who underwent PCI with DES implantation were consecutively enrolled from January 2013 to December 2013 at Fuwai Hospital, National Center for Cardiovascular Diseases (Beijing, China) without any exclusion criteria. The study was conducted according to the principles of the Declaration of Helsinki, and its protocol was approved by the hospital's ethical review board (Fuwai Hospital & National Center for Cardiovascular Diseases, Beijing, China). All patients provided written informed consent for prospective follow-up before the intervention. In brief, we used the TWILIGHT inclusion criteria to identify the "TWILIGH-like" population.[3,4] A total of 8,358 patients fulfilling the "TWILIGHT-like" criteria were identified, who had at least one clinical and one angiographic feature associated with a high risk of ischemic or bleeding events. Clinical criteria included ≥65 years, female gender, troponin-positive ACS, established vascular disease, DM that was being treated with medication, and chronic kidney disease (CKD). The angiographic criteria for high risk were multivessel coronary artery disease (CAD), total stent length >30 mm, a bifurcation lesion treated with 2 stents, thrombotic target lesion, left main (≥50%) or proximal left anterior descending (≥70%) lesion, and calcified target lesions requiring atherectomy. This study analyzed data of 3,041 high-risk patients who underwent complex PCI. Of these, 2,692 patients who were free from major ischemic or bleeding events (all-cause death, MI, stent thrombosis, stroke, repeat revascularization, or Bleeding Academic Research Consortium major bleeding) at 12 months follow-up. We further excluded 15 patients were not followed up for 12 months after the index procedure. Finally, 2,677 "TWILIGHT-like" high-risk patients who underwent complex PCI who met the selection criteria were divided into 2 groups based on duration of DAPT (aspirin+clopidogrel) use: DAPT >12-month group and DAPT≤12-month group (Figure 1). Landmark analysis was performed to classify patients into treatment groups based on 12-month antiplatelet treatment after PCI and to evaluate prognosis from the landmark time point.

PCI procedure and best available medical therapy were performed in accordance with the standard procedural guidelines at the time of each procedure.[14,15] Detailed information on procedures is shown in Supplementary Methods. Information about demographics, medication, laboratory, procedural, and outcome data was recorded prospectively in our dedicated PCI registry by independent research personnel. Patients were routinely followed up at 1, 6, and 12 months after the index procedure and annually thereafter. Follow-up data were collected through medical records, telephone communications, or face-to-face interviews after hospital discharge by well-trained cardiologists who were blind to the purpose of the present study, until death occurred or up to the last day of the follow-up period. Patients were advised to return for coronary angiography if indications of ischemic events occurred. Adherence to antiplatelet medication was routinely assessed at each time of follow-up. To identify the status of antiplatelet therapy, the date and duration of prescribed antiplatelet medications were collected from the electronic prescribing system at Fuwai Hospital.

The definition of complex PCI in the current analysis are based on a modified version of previously published criteria, which have also been described in part in other clinical studies.[8,9,14,16,17] PCI was defined as complex PCI when at least one of the following features were met: ≥3 lesions treated, ≥3 stents implanted, 3 coronary vessels treated, total stent length >60 mm, bifurcation with 2 stents implanted, chronic total occlusion (CTO) as target lesion, left main as target vessel, use of any atherectomy device, or surgical bypass graft.

The primary efficacy end point was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) during follow-up, defined as a composite of all-cause death, MI, or stroke. The primary safety end point was clinically relevant bleeding, which was determined as Bleeding Academic Research Consortium type 2, 3, or 5 bleeding. The net clinical benefit outcome was the composite of all-cause death, MI, stroke, or clinically relevant bleeding. Secondary end points included all-cause death, cardiovascular death, MI, definite/probable ST, stroke, and ischemic stroke. Definitions for the end points were described in Supplementary Methods.

Continuous variables are presented as mean ± SD or median with interquartile range as appropriate, and compared using Student *t* tests or Wilcoxon rank-sum test, respectively. Categorical variables are presented as frequencies and percentages and compared using chi-square or Fisher exact tests as appropriate. Cumulative incidence was estimated by the Kaplan-Meier method and differences between the DAPT >12-month and DAPT ≤12-month groups were assessed with the log-rank test. We considered 3 approaches to estimate associations between DAPT duration and clinical outcomes: multivariable Cox model, propensity score (PS)-matched analysis, and inverse probability of treatment weighting (IPTW). The methodological details of multivariable Cox model, PS-matching, and IPTW analyses are provided in Supplementary Methods. Risks of MACCE between >12-month DAPT and ≤12-month DAPT across the individual components of complex PCI definition and stratified by number of complex PCI criteria fulfilled (1, 2, or 3 or more features) were also analyzed. All tests were two-sided and a p value of <0.05 was considered to be statistically significant. Statistical analyses were conducted using SPSS version 22 (IBM, Armonk, NY) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Within the complex PCI cohort, the mean age of high-risk complex PCI patients was 58.9 ± 10.0 years and majority were men (76.8%), with had high prevalence of common

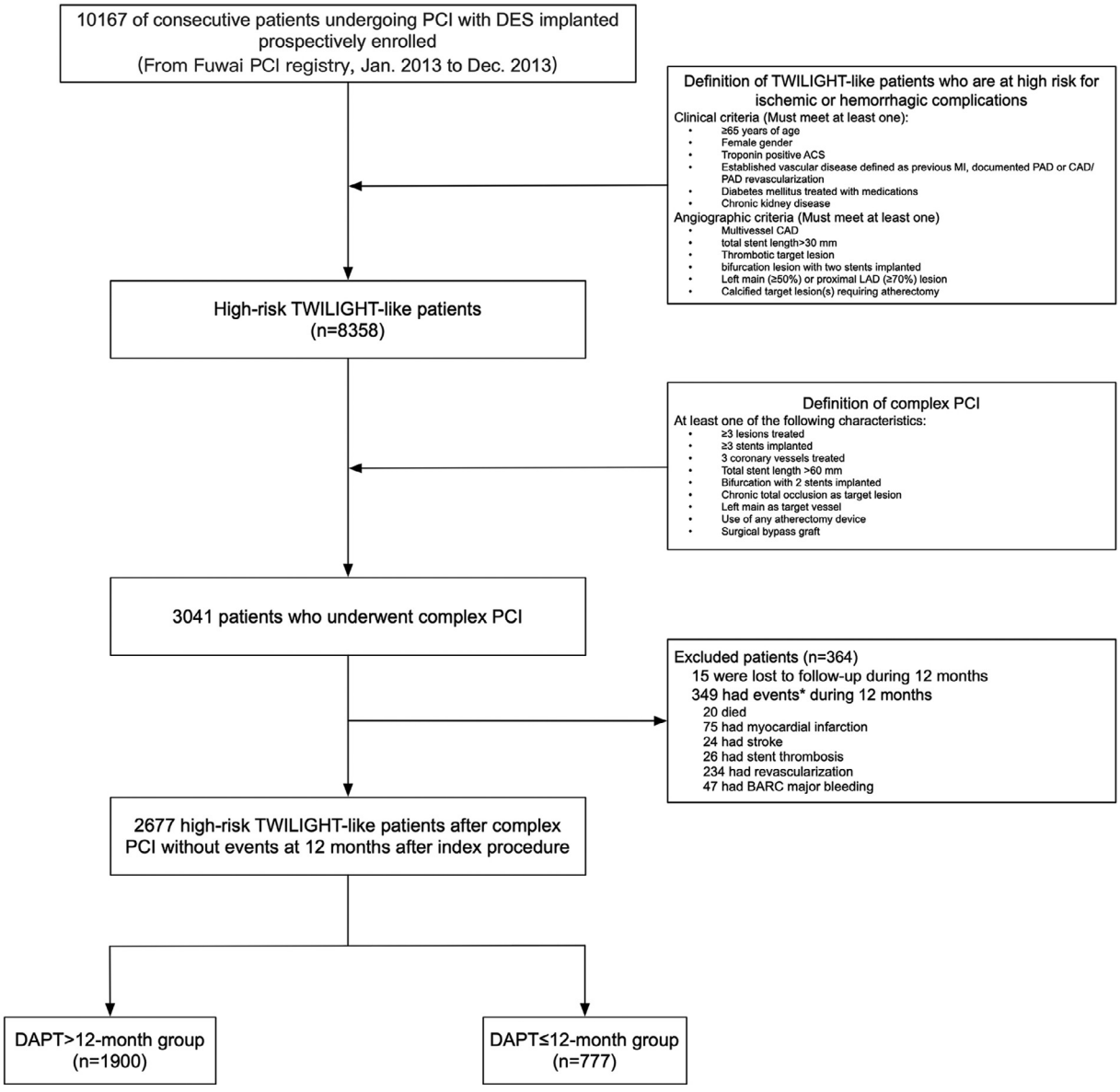

Figure 1. Subject flowchart.
ACS, acute coronary syndrome; BARC, bleeding Academic Research Consortium; CAD, coronary artery disease; DES, drug-eluting stent; DAPT, dual antiplatelet therapy; LAD, left anterior descending; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; *Subjects may have >1 event.

cardiovascular risk factors. The prevalence of each component of the complex PCI definition is indicated in Figure 2. Of 2,677 high-risk TWILIGHT-like patients who underwent complex PCI who were event-free at 12 months after index procedure, 1,900 patients received DAPT >12-month (DAPT ≥12-month group) and 777 patients did not (DAPT ≤12-month group). The mean duration of DAPT was 666 days (standard error [SE] 3.81) in the DAPT >12-month group and 351 days (SE 2.04) in the DAPT ≤12-month group. As seen in Tables 1 and 2, no differences were noted between treatment groups on baseline clinical and procedural characteristics. The 2 DAPT duration groups were closely balanced on all baseline covariates after propensity score matching and IPTW analysis, with the absolute standardized mean difference below 10% for all covariates (Supplementary Tables 1 and 2).

The median follow-up duration was 29.1 months (interquartile range: 26.6 to 31.1 months). Follow-up data were available for 99.3% (2,659 of 2,677) of the eligible patients at 24 months after index procedure. There were 73 (2.7%) patients who had the primary efficacy outcome event, including 28 all-cause death, 16 MI, and 41 strokes. The clinical outcomes according to DAPT duration in high-risk TWILIGHT-like patients after complex PCI are presented in Figure 3 and Table 3. By the multivariable Cox regression analysis, DAPT >12 months was associated with lower rates of MACCE in comparison with DAPT ≤12 months (1.9% vs 4.8%; HR_{adj} 0.374; 95% CI 0.235 to 0.595; p <0.001), which was mainly driven by all-cause reduction (0.3% vs 2.8%; HR_{adj} 0.105; 95% CI 0.042 to 0.261; p <0.001). There were large risk reductions in individual end points, including a 90% reduction in cardiovascular

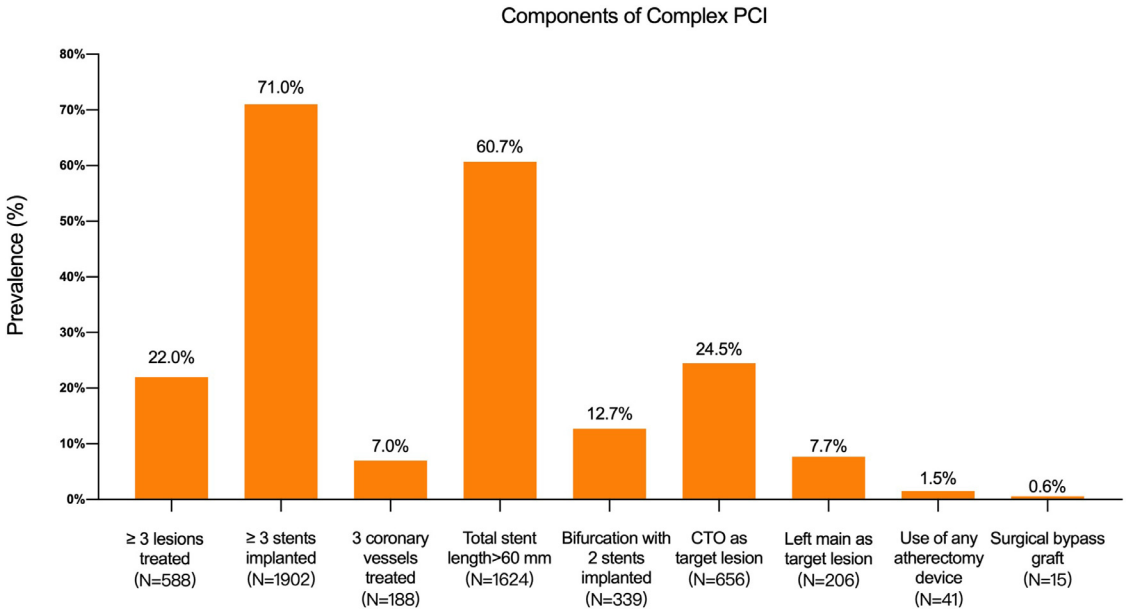

Figure 2. Prevalence of complex PCI components in the overall population.
The definition of complex PCI was defined when at least one of the following features were met: ≥3 lesions treated, ≥3 stents implanted, 3 coronary vessels treated, total stent length >60 mm, bifurcation with 2 stents implanted, chronic total occlusion (CTO) as target lesion, left main as target vessel, use of any atherectomy device, or surgical bypass graft. ≥3 stents implanted was the most common characteristic in complex PCI patients while surgical bypass graft as target lesion was the least common.

death (0.2% vs 1.5%; HR_{adj} 0.095; 95% CI 0.026 to 0.344; p <0.001) and a 76% reduction in definite/probable ST (0.3% vs 0.9%; HR_{adj} 0.235; 95% CI 0.072 to 0.770; p = 0.017) with DAPT >12 months than DAPT ≤12 months. In contrast, the risk of clinically relevant bleeding was statistically similar between the 2 regimens (1.1% vs 0.8%; HR_{adj} 1.189; 95% CI 0.474 to 2.984; p = 0.713). Finally, an analysis of net clinical benefit outcome (composite of death, MI, stroke, or clinically relevant bleeding) significantly favored a >12-month DAPT strategy (2.8% vs 5.5%; HR_{adj} 0.468; 95% CI 0.312 to 0.702; p <0.001).

These results were consistently observed in PS-matching and IPTW analysis. In the PS-matched cohort, we observed a lower incidence of MACCE in DAPT >12-month group compared with DAPT ≤12-month group ($HR_{matched}$ 0.292 [95% CI 0.151 to 0.561]; HR_{IPTW} 0.356 [95% CI 0.225 to 0.562]). As well, extended DAPT continued to be associated with a lower risk of all-cause death with directional consistency for cardiac death, definite/probable ST, and stroke in the PS-matched and IPTW cohort. Clinically relevant bleeding ($HR_{matched}$ 1.577 [95% CI 0.577 to 4.312]; HR_{IPTW} 1.239 [95% CI 0.502 to 3.059]) was numerically higher but not statistically different for longer than 12-month DAPT in comparison with ≤12-month DAPT. The effect of DAPT >12 months versus DAPT ≤12 months for primary composite outcome of all-cause death, MI, or stroke was consistent across the components of the complex PCI definition (Figure 4). There were also no differences in results depending on how many complex PCI criteria a given patient had (Figure 4). The direction and magnitude of the effect for DAPT >12-month compared with DAPT ≤12 months on clinical outcomes were similar in patients with and without ACS, with no evidence of statistical interaction (Supplementary Table 4) (all $P_{interaction}$>0.05).

Discussion

This analysis, using a large-scale, prospective, real-world registry, is the first assessment describing the efficacy and safety of a prolonged DAPT regimen in high ischemic or hemorrhagic risk patients who underwent complex PCI. This study has several principle findings as follows: (1) DAPT continuation beyond 12 months with clopidogrel and aspirin, as compared with ≤12-month DAPT, was associated with a lower risk of MACCE and cardiovascular mortality over a median of 2.4 years of follow-up; (2) There was no apparent increase in the risk of clinically relevant bleeding for patients treated with DAPT >12 months; (3) The potential net clinical benefit suggested that extension of DAPT beyond 12 months may have a favorable benefit-risk ratio in this high-risk population; (4) These favorable prognostic findings for DAPT >12 months with regard to ischemic and bleeding outcomes were maintained after PS-matching and IPTW analysis and were consistent across the individual components and the numbers of complex PCI definition. Overall, these findings offer insight into the need for longer-term maintenance of DAPT even in "TWILIGHT-like" cohort of complex PCI patients who are event free during the first year after PCI to prevent late atherothrombotic events.

The present analysis contributes to the few studies that have examined the effectiveness and safety of prolonged DAPT among complex PCI patients. An analysis from a pooled dataset of 6 randomized trials (n = 9,577) showed

Table 1.
Baseline clinical characteristics in high-risk TWILIGHT-like patients after complex PCI according to DAPT duration

Variable	DAPT >12 months (n = 1,900)	DAPT ≤12 months (n = 777)	p value
Age (years)	58.84 ± 9.88	59.22 ± 10.29	0.523
Men	1452 (76.4%)	603 (77.6%)	0.510
Body mass index (kg/m^2)	26.13 ± 3.18	25.89 ± 3.29	0.733
Hypertension	1264 (66.5%)	527 (67.8%)	0.517
Hyperlipidemia	1299 (68.4%)	512 (65.9%)	0.214
Chronic kidney disease	86 (4.5%)	33 (4.2%)	0.750
Diabetes mellitus	896 (47.2%)	364 (46.8%)	0.884
Insulin-treated	229 (25.6%)	87 (23.9%)	0.539
Current smoker	1107 (58.3%)	440 (56.6%)	0.437
Anemia	67 (3.5%)	26 (3.3%)	0.817
Peripheral artery disease	60 (3.2%)	24 (3.1%)	0.926
Prior myocardial infarction	453 (23.8%)	182 (23.4%)	0.817
Prior PCI	434 (22.8%)	166 (21.4%)	0.405
Prior CABG	105 (5.5%)	41 (5.3%)	0.796
Prior stroke	216 (11.4%)	89 (11.5%)	0.949
Prior major bleeding event	14 (0.7%)	7 (0.9%)	0.662
Left ventricular ejection fraction (%)	62.16 ± 7.55	62.35 ± 7.45	0.265
Indication for PCI			0.145
Stable CAD	732 (38.5%)	276 (35.5%)	
ACS	1168 (61.5%)	501 (64.5%)	
UA/NSTEMI	915 (48.2%)	390 (50.2%)	0.339
STEMI	253 (13.3%)	111 (14.3%)	0.506
Hemoglobin (g/dL)	14.24 ± 1.56	14.18 ± 1.51	0.746
Platelet count (10^9/L)	205.38 ± 53.41	203.17 ± 51.68	0.478
White blood cell count (10^9/L)	6.81 ± 1.64	6.72 ± 1.58	0.891
DAPT score	1.97 ± 1.29	1.94 ± 1.30	0.739
PARIS thrombotic risk score	2.64 ± 1.68	2.68 ± 1.63	0.865
PARIS bleeding risk score	3.73 ± 2.06	3.83 ± 2.18	0.137
PRECISE-DAPT score	10.88 ± 8.34	11.25 ± 9.07	0.189
Medication during hospitalization			
Aspirin	1879 (98.9%)	770 (99.1%)	0.637
Clopidogrel	1866 (98.2%)	769 (99.0%)	0.151
Beta-blocker	1756 (92.4%)	710 (91.4%)	0.363
Calcium channel blockers	955 (50.3%)	376 (48.4%)	0.379
Statin	1830 (96.3%)	750 (96.5%)	0.793

Values are mean ± SD for continuous variables, and n (%) for categorical variables. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PARIS, patterns of nonadherence to antiplatelet regimen in stented patients; STEMI, ST-segment elevation myocardial infarction; and UA, unstable angina.

that long-term DAPT with aspirin and clopidogrel (≥12 months) provided significant reduction in major ischemic events compared with 3 or 6 months of DAPT followed by aspirin alone in patients who underwent complex PCI (>50% subjects with multivessel disease) with mostly new-generation DES.[8] However, there was an accompanying increase in major bleeding with extended DAPT despite of the anti-ischemic benefit. In the DAPT trial, among patients not sustaining major bleeding or ischemic events 12 months after PCI, prolongation of DAPT beyond 12 months after DES implantation reduced its coprimary end points of MACCE and ST in comparison with aspirin alone among complex coronary artery target lesions without significantly increasing the risk of moderate/severe bleeding,[9] findings analogous to our results. In a post hoc analysis of the PRECISE-DAPT population, patients who underwent complex PCI and were not at high bleeding risk could benefit from a long course of DAPT (i.e., 12 or 24 months) compared with that of short-term DAPT (i.e., 3 or 6 months) with no apparent tradeoff in bleeding, which ultimately presented an favorable net clinical benefit outcome.[18] Considering that procedural complexity is a key clinical inclusion criterion in "TWILIGHT-like" patients, in this context, we elected to focus on the large subgroup of patients fulfilling complex PCI criteria in high-risk "TWILIGHT-like" patients who represented not only bleeding risk but also ischemic risk features.

Our findings are noteworthy in light of the high-risk profile for both thrombotic and hemorrhagic complications of this ever-growing cohort of complex PCI patients in real-world clinical practice. The present analysis extended previous evidence by showing that although clinically relevant bleeding was numerically increased, the benefit of ischemic events and the net clinical benefit outcome in high-risk patients after complex PCI treated with long-term (>12 months) compared with short-term DAPT (≤12 months) is relevant and underlines the opportunity to prolonging DAPT in this subset of patients. These findings may be explained by some plausible hypotheses. First, given that

Table 2.
Procedural characteristics in high-risk TWILIGHT-like patients after complex PCI according to DAPT duration

	DAPT >12 months (n = 1,900)	DAPT ≤12 months (n = 777)	p value
Multivessel coronary artery disease	1684 (88.6%)	678 (87.3%)	0.317
Target coronary artery			
Left main	152 (8.0%)	54 (6.9%)	0.355
Left anterior descending	1567 (82.5%)	644 (82.9%)	0.800
Left circumflex	704 (37.1%)	303 (39.0%)	0.346
Right coronary	792 (41.7%)	311 (40.0%)	0.429
Bypass graft	11 (0.6%)	4 (0.5%)	0.840
Total lesion length (mm)	64.94 ± 29.80	63.39 ± 27.46	0.084
Number of vessels treated	1.62 ± 0.62	1.62 ± 0.61	0.467
Number of lesions treated			0.928
1	603 (31.7%)	246 (31.7%)	
2	884 (46.5%)	357 (45.9%)	
≥3	413 (21.7%)	174 (22.4%)	
Number of stents implanted	3.01 ± 1.09	2.93 ± 1.02	0.138
Total stent length (mm)	68.89 ± 28.94	67.80 ± 26.72	0.151
Mean stent diameter (mm)	2.90 ± 0.52	2.87 ± 0.55	0.318
Target lesion morphology			
Bifurcation lesion	425 (22.4%)	170 (21.9%)	0.782
Chronic total occlusion	474 (24.9%)	182 (23.4%)	0.405
In-stent restenosis	100 (5.3%%)	35 (4.5%)	0.416
Severe calcification	120 (6.3%)	47 (6.0%)	0.796
Thrombotic lesion	86 (4.5%)	35 (4.5%)	0.980
Type B2 or C lesion	1746 (91.9%)	726 (93.4%)	0.173
SYNTAX score	15.47 ± 8.20	15.87 ± 8.31	0.240
Type of DES implanted			0.977
First-generation DES	212 (11.2%)	87 (11.2%)	
Second-generation DES	1688 (88.8%)	690 (88.8%)	
Radial artery access	1702 (89.6%)	696 (89.6%)	0.998
Use of intravascular ultrasound	191 (10.1%)	80 (10.3%)	0.850
Glycoprotein IIb/IIIa use	393 (20.7%)	171 (22.0%)	0.446

Values are mean ± SD for continuous variables, and n (%) for categorical variables. DES, drug-eluting stent; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

ACS patients with PCI complexity are at further heightened risk for recurrent cardiovascular events including death,[19] more than 60% of complex PCI patients in our study are coexistent with ACS and thus constitute a very high-risk group of patients for ischemic complications post-PCI. The PROSPECT study has shown that recurrent coronary events occurring after ACS during follow-up were nearly equally divided between those related to initially treated (culprit) lesions and those related to previously untreated (nonculprit) lesions.[20] In the TRITON-Thrombolysis in Myocardial Infarction (TIMI) 38 study, over 80% of ischemic events occurring after 1 month were unrelated to the stented lesion, but were rather spontaneous (non-ST or nonprocedure-related) events.[21] Extended treatment with DAPT beyond 1 year improved late-phase cardiovascular outcomes in 12,844 patients with ACS, predominately by reducing de novo atherothrombotic ischemic events. Accordingly, the benefit of prolonged DAPT observed in our study might derive from the prevention of de novo atherothrombotic events at nonculprit lesions. Second, the presence of concomitant multivessel CAD (88.2%) in patients who underwent complex PCI implies a greater predisposition to native plaque progression and acute changes with subsequent atherothrombosis.[22] Indeed, the PEGASUS-TIMI 54 trial has revealed that patients with previous MI and multivessel CAD treated with long-term DAPT with ticagrelor and aspirin were afforded significant reductions in major adverse cardiovascular events and coronary events, including death.[23] Likewise, Lee et al [24] reported that 12-month DAPT was associated with a lower risk of major adverse cardiovascular events and MI compared with shorter-duration (6-month) DAPT among patients with multivessel CAD, which favored the longer-term maintenance of DAPT in this high-risk subset of patients. Third, complex percutaneous coronary revascularization procedures may be linked with a greater likelihood of incomplete revascularization and residual CAD, thus affecting recurrent cardiac ischemic events and mortality in the setting of multivessel disease.[25,26] Collectively, prolonged DAPT may protect from the previously mentioned pathophysiological mechanisms in high-risk complex PCI patients. Taken together, our findings provide preliminary evidence that longer than 12-month DAPT with clopidogrel and aspirin potentially might balance ischemic and bleeding risks, thereby resulting in a net clinical benefit in “TWILIGHT-like” high-risk patients after complex PCI.

Our study does have limitations. First, the Fuwai PCI study is a large, prospective, observational registry and has the inherent limitations of observational data sets. Although outcomes were collected prospectively, this is a

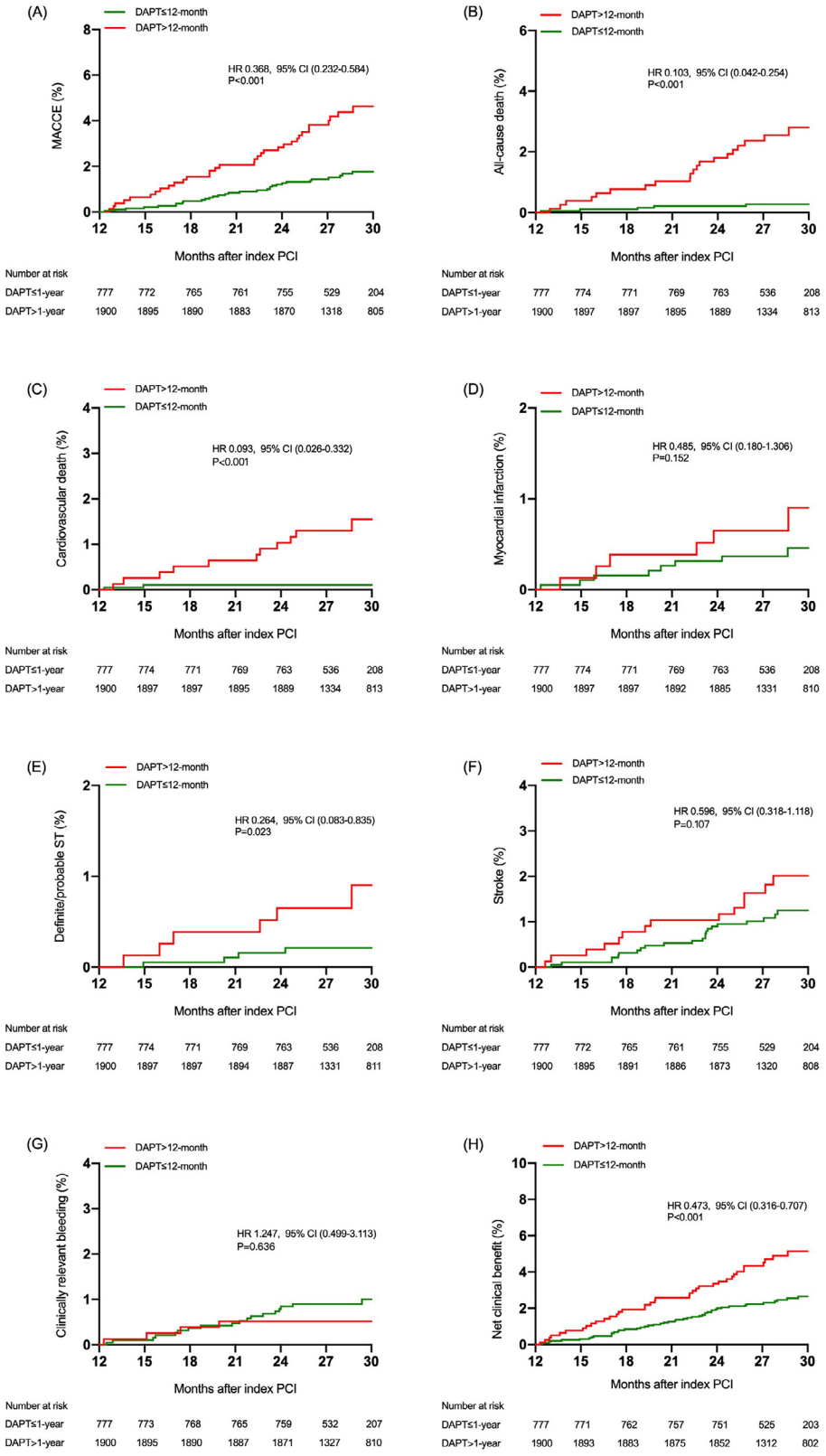

Figure 3. Cumulative incidence of clinical outcomes according to DAPT duration.
Kaplan-Meier event curves for *(A)* major adverse cardiac and cerebrovascular events (MACCE), *(B)* all-cause death, *(C)* cardiovascular death, *(D)* myocardial infarction, *(E)* definite/probable stent thrombosis, *(F)* stroke, *(G)* clinically relevant bleeding, and *(H)* Net clinical benefit outcome, according to the duration of DAPT (DAPT >12-month versus DAPT ≤12-month).

Table 3.
Comparison of clinical outcomes between >12-month DAPT and ≤12-month DAPT in high-risk TWILIGHT-like patients after complex PCI

	DAPT > 12 months (n = 1,900)	DAPT ≤12 months (n = 777)	Univariate analysis		Multivariable analysis		PS matching Analysis		IPTW analysis	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
MACCE	36 (1.9%)	37 (4.8%)	0.368 (0.232-0.584)	<0.001	0.374 (0.235-0.595)	<0.001	0.292 (0.151-0.561)	<0.001	0.356 (0.225-0.562)	<0.001
Cardiovascular death, myocardial infarction, or ischemic stroke	32 (1.7%)	27 (3.5%)	0.448 (0.268-0.748)	0.002	0.455 (0.270-0.765)	0.003	0.364 (0.180-0.737)	0.005	0.425 (0.256-0.706)	0.001
All-cause death	6 (0.3%)	22 (2.8%)	0.103 (0.042-0.254)	<0.001	0.105 (0.042-0.261)	<0.001	0.085 (0.020-0.361)	0.001	0.102 (0.041-0.256)	<0.001
Cardiovascular death	3 (0.2%)	12 (1.5%)	0.093 (0.026-0.332)	<0.001	0.095 (0.026-0.344)	<0.001	0.078 (0.010-0.601)	0.014	0.095 (0.026-0.342)	<0.001
Myocardial infarction	9 (0.5%)	7 (0.9%)	0.485 (0.180-1.306)	0.152	0.459 (0.167-1.259)	0.130	0.530 (0.155-1.818)	0.313	0.475 (0.179-1.259)	0.134
Definite/probable ST	5 (0.3%)	7 (0.9%)	0.264 (0.083-0.835)	0.023	0.235 (0.072-0.770)	0.017	0.398 (0.103-1.546)	0.183	0.261 (0.084-0.812)	0.019
Stroke	25 (1.3%)	16 (2.1%)	0.596 (0.318-1.118)	0.107	0.584 (0.309-1.106)	0.099	0.378 (0.154-0.926)	0.033	0.537 (0.291-0.993)	0.047
Ischemic stroke	23 (1.2%)	15 (1.9%)	0.583 (0.304-1.119)	0.105	0.583 (0.301-1.130)	0.110	0.402 (0.162-0.994)	0.049	0.520 (0.276-0.982)	0.044
Clinically relevant bleeding	20 (1.1%)	6 (0.8%)	1.247 (0.499-3.113)	0.636	1.189 (0.474-2.984)	0.713	1.577 (0.577-4.312)	0.375	1.239 (0.502-3.059)	0.642
Net clinical benefit	54 (2.8%)	43 (5.5%)	0.473 (0.316-0.707)	<0.001	0.468 (0.312-0.702)	<0.001	0.474 (0.284-0.790)	0.004	0.462 (0.310-0.688)	<0.001

Values are number of events (%) unless otherwise indicated. Multivariable Cox proportional hazard regression model, propensity-score matched cohort, and inverse probability of treatment weighting method were used to adjust for baseline differences between comparative groups. Variables entered into multivariable Cox models were as follows: for ischemic outcomes: age, gender, current smoker, hypertension, diabetes mellitus, CKD, ACS, LVEF, PAD, previous MI, previous revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), multivessel CAD, total lesion length, SYNTAX score, and type of DES implanted; for clinically relevant bleeding: age, gender, body mass index, diabetes mellitus, CKD, ACS, prior major bleeding event, and anemia (hemoglobin <12 g/dl for men and <11 g/dl for women); for net clinical benefit outcome: all variables included in the multivariable model for ischemic outcomes and clinically relevant bleeding.

ACS, acute coronary syndrome; CI, confidence interval; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral vascular disease; PARIS, patterns of nonadherence to antiplatelet regimen in stented patients; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; ST, stent thrombosis.

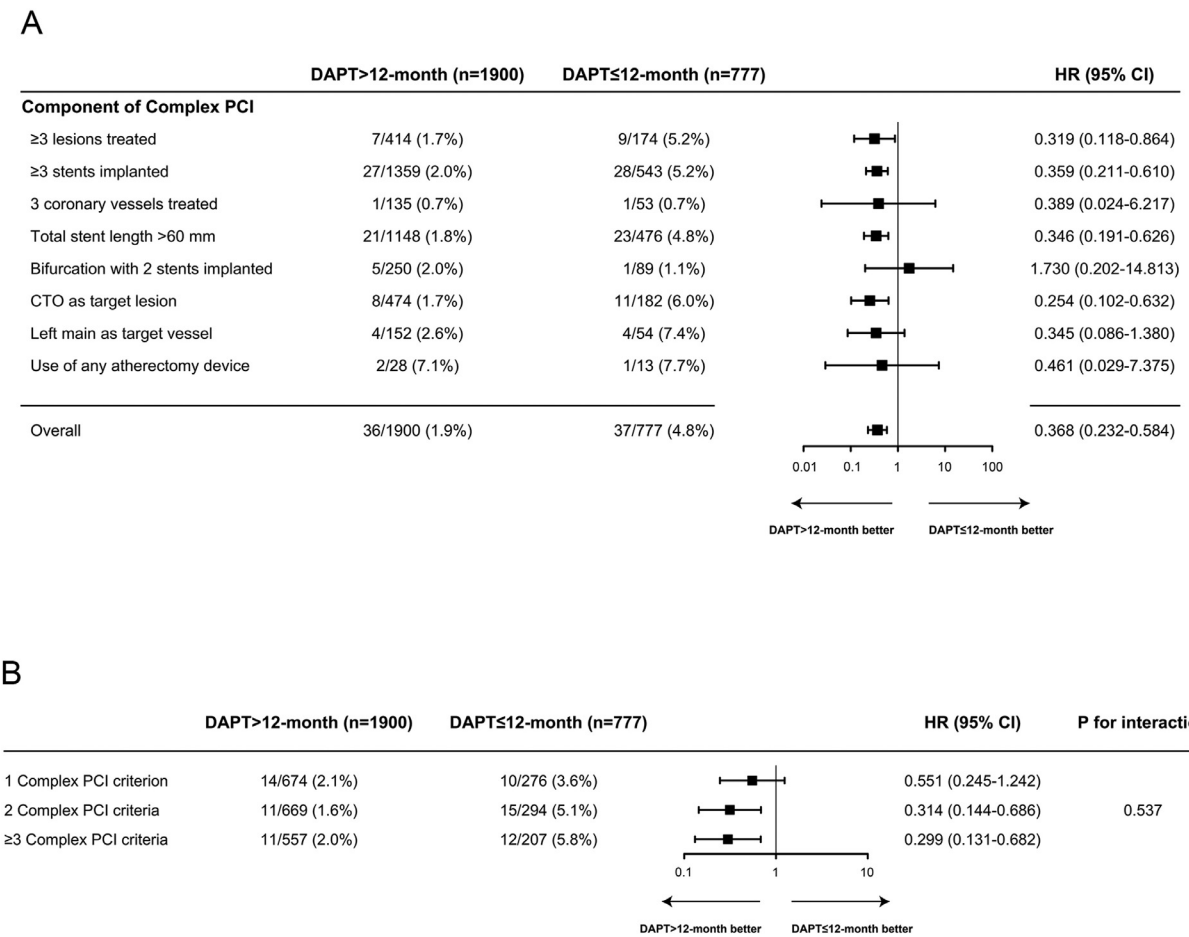

Figure 4. Comparative unadjusted hazard ratios of MACCE between the DAPT >12-month and DAPT ≤12-month group *(A)* across the individual components of the complex PCI definition and *(B)* stratified by number of complex PCI criteria fulfilled in the overall population.
The effect of DAPT >12 months versus DAPT ≤12 months for the end point of MACCE was consistent across the components of the complex PCI definition as well as when stratified according to progressive number of complex PCI criteria fulfilled. CI, confidence interval; CTO, chronic total occlusion; HR, hazard ratio; PCI, percutaneous coronary intervention.

retrospective analysis reflecting the experience of a large-volume single center. Hence, the current findings should be considered hypothesis-generating. Second, the duration of DAPT was not randomly assigned but was determined at the discretion of the attending physician according to clinical judgment. Although we rigorously adjusted for differences in baseline characteristics to overcome the potential bias that can influence the study outcome using multivariable Cox models, PS-matching, and IPTW analysis, unmeasured confounders (e.g., socioeconomic status) may have affected our results. Third, the incidences of MACCE, cardiovascular death, MI, or stent thrombosis were low when compared with adequately powered DAPT trial, which excluded patients with adverse clinical events for at least 12 months.[27] Since statistical power of this study might be low because of low event rate for individual end point, our findings were at risk for type II error to demonstrate significant differences in comparisons between DAPT treatment groups and cannot draw definitive conclusions. Fourth, the present results are not generalizable to all patients after PCI due to the inclusion end exclusion criteria of this study. Last, although more than 60% of patients enrolled in this study were ACS, the general use of new antiplatelet agents (ticagrelor and prasugrel) was unavailable during the time of enrollment in China; as a result all patients were treated with clopidogrel. Whether our results apply to the potent P2Y12 inhibitors remains to be established.

In conclusion, among high-risk "TWILIGHT-like" patients who underwent complex PCI and who remained free from major ischemic and bleeding events 12 months after coronary stenting, continuation of DAPT with clopidogrel and aspirin beyond 12 months was associated with a positive net clinical benefit, as it was associated with a reduction in the incidence of ischemic events without trade-off in the risk of clinically relevant bleeding.

Credit Author Statement

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Disclosures

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.033.

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