Benefits and Risks of Prolonged Duration Dual Antiplatelet Therapy (Clopidogrel and Aspirin) After Percutaneous Coronary Intervention in High-Risk Patients With Diabetes Mellitus

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The efficacy and safety of prolonged (>1-year) dual antiplatelet therapy (DAPT) duration in high-risk patients with diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI) remain unknown. All patients undergoing PCI at Fuwai hospital between January 2013 and December 2013 were prospectively enrolled into the Fuwai PCI registry. A total of 3,696 high-risk diabetics patients with at least one additional atherothrombotic risk factor were screened for inclusion. The primary efficacy outcome was the composite of all-cause mortality, myocardial infarction, or stroke. The median follow-up duration was 887 days. 69.8% of DM patients were on DAPT at 1 year without discontinuation. Based on multivariate Cox regression model and inverse probability of treatment weighting (IPTW) analysis, long-term (>1-year) DAPT reduced the risk of primary efficacy outcome (1.7% vs 4.1%; adjusted hazard ratio [adjHR]: 0.382, 95% confidence interval [CI]: 0.252 to 0.577; IPTW-HR: 0.362 [0.241 to 0.542]), as well as cardiovascular death and definite/probable stent thrombosis, compared with short-course (≤1-year) DAPT. Risk of the safety end point of clinically relevant bleeding (adjHR: 0.920 [0.467 to 1.816]; IPTW-HR: 0.969 [0.486 to 1.932]) was comparable between longer DAPT and shorter DAPT. A lower number of net clinical benefit adverse outcomes was observed with >1-year DAPT versus ≤1-year DAPT (adjHR: 0.471 [0.331 to 0.671]; IPTW-HR: 0.462 [0.327 to 0.652]), which appeared increasingly favorable in those with multiple atherothrombotic risk characteristics. In high-risk patients with DM receiving PCI who were event free at 1 year, DAPT prolongation resulted in significant reduction in the risk of ischemic events not offset by increase of clinically meaningful bleeding events, thereby achieving a net clinical benefit. Extending DAPT beyond the period mandated by guidelines seems reasonable in high-risk DM patients not deemed at high bleeding risk. **(Am J Cardiol 2021;142:14−24)**

Dual antiplatelet therapy (DAPT) consisting of aspirin and $P2Y_{12}$ receptor inhibitor, is indicated to prevent subsequent coronary thrombotic events including stent thrombosis, after percutaneous coronary intervention (PCI).[1] Questions remain, however, about the optimal timing of DAPT following drug-eluting stent (DES) placement.[2] Long-term DAPT reduces rates of adverse clinical and thrombotic events, but these effects are achieved at the expense of an increased risk bleeding.[3,4] Hence, a personalized approach is advisable when deciding upon longer courses of DAPT duration, wherein clinicians are warranted to identify patients who are carefully assessed to be at high ischemic risk but low bleeding risk. Diabetes mellitus (DM) is frequently encountered in patients who underwent PCI and contributes to a prothrombotic state and residual cardiovascular risk,[5] posing unique challenges in the antiplatelet management of such patients due to a higher risk for ischemic events and mortality than patients without DM.[6,7] Moreover, diabetic patients often have many other concomitant co-morbidities (e.g., multivessel disease, chronic kidney disease) that predispose them at high ischemic risk, which suggests that this high-risk population may derive particular benefit from prolonged use of DAPT. However, the most appropriate DAPT regimen for high-risk diabetic patients in a real-world context remains unclear. In the present analysis, we assessed the efficacy and safety of prolonged term (>1-year) DAPT versus shortening DAPT to ≤1-year in a large and contemporary PCI

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cohort of high-risk patients with DM and at least one additional atherothrombotic risk factor.

Methods

Fuwai registry was a large single-center, prospective, observational study that enrolled a total of 10,167 consecutive patients who underwent PCI with at least one DES between January 2013 and June December 2013 from Fuwai Hospital (National Center for Cardiovascular Diseases, Beijing, China). This prospective PCI registry complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee at Fuwai Hospital, Beijing, China. All eligible patients signed written informed consent for participation in this registry. For purposes of the present analysis, we enrolled high-risk patients with DM, in whom diabetic patients are needed to have at least one additional high-risk features (age ≥65 years, current smoking, chronic renal dysfunction with estimated glomerular filtration rate <60 ml/min, heart failure, peripheral artery disease [PAD], history of ischemic stroke, history of myocardial infarction [MI], multivessel coronary artery disease [CAD]). The enrichment criteria of high-risk features were captured based on PEGASUS-TIMI 54 and COMPASS trials.[8,9] Diabetic patients were defined as patients who had been treated with oral hypoglycemic agents or insulin or those with hemoglobin A1c (HbA1c) ≥6.5% at baseline, based on the current guidelines.[10] From the overall population, 4,097 high-risk patients with DM were identified. Among 4,076 high-risk diabetic patients followed-up for 1 year, 382 patients who experienced death from any cause, MI, stroke, revascularization, definite or probable stent thrombosis, or Bleeding Academic Research Consortium 2, 3, or 5 bleeding were excluded. A total of 3,696 high-risk patients with DM who were event-free at 1 year were finally included in the current analysis (Figure 1).

PCI was done according to standard techniques at the discretion of the treating physician (Supplementary Methods).[11] After PCI, DAPT (clopidogrel + aspirin) was recommended for at least 1 year (with longer duration of use at the discretion of the physician), whereas aspirin was continued indefinitely. The decision to discontinue or remain on DAPT after 1 year was made at the discretion of the patient's physician (and possibly influenced by the patient), wherein the individualized risks of ischemic versus bleeding events are carefully considered for each patient. Baseline and procedural characteristics, findings of coronary angiography, clinical diagnosis, and clinical events were systematically obtained by independent research personnel using standardized forms at the time of index

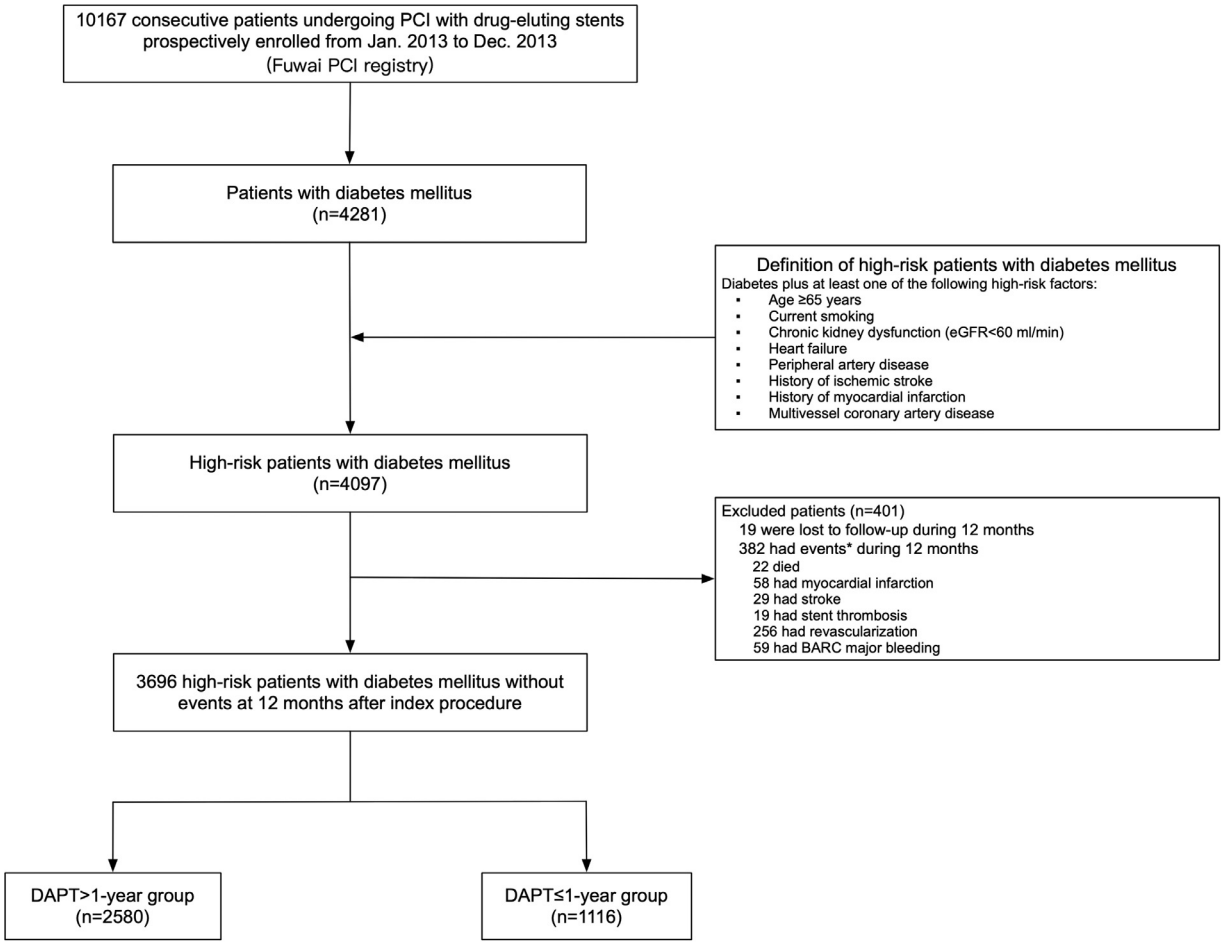


Figure 1. Subject flowchart. ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; PAD = peripheral artery disease; PCI = Percutaneous coronary intervention. *Subjects may have >1 event.

hospitalization for PCI. Clinical follow-up was performed at 1 month, 6 months, and 12 months after the index treatment and then annually thereafter through out-patient clinical visit, telephone calls, or medical records review. Dedicated independent clinical research coordinators collected and input all data obtained during the follow-up visits. At each visit, the data pertaining to patient clinical status, all interventions received, outcomes, and adverse events were recorded. In particular, information on the antiplatelet medication (use of aspirin or a $P2Y_{12}$ inhibitor) was assessed at each follow-up.

The primary efficacy end point was 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 the Bleeding Academic Research Consortium type 2, 3, or 5 bleeding. The net clinical benefit outcome was defined as all-cause death, MI, stroke, or clinically relevant bleeding. Secondary end points and end points definitions were in the Supplementary Methods. An independent clinical events committee blinded to outcome data monitored and adjudicated all in-hospital and postdischarge events by using relevant medical records.

Baseline and procedural characteristics are presented with mean ± SD or numbers with percentages (p-values from Student's *t* test for continuous variables, chi-square test or Fisher's exact test for binary variables, comparing DAPT >1-year versus DAPT ≤1-year). Cox regression models and Kaplan-Meier cumulative events curves were used to compare DAPT >1-year versus DAPT ≤1-year. Baseline variables used for multivariable Cox regression adjustment were shown in the Supplementary Methods. To reduce the impact of treatment selection bias and potential confounding in this observational study, an inverse probability of treatment weighted (IPTW) analysis was applied. The propensity score was defined as the probability of duration of DAPT treatment subjective to observed baseline characteristics, and IPTW method on the basis of the propensity score was used to adjust for confounding factors in weighted Cox regression models. The variables used for propensity models and detailed methods of IPTW analysis were provided in the Supplementary Methods. Additional exploratory analyses were performed to evaluate treatment effects on MACCE, clinically relevant bleeding and net clinical benefit outcomes in relation to risk factor burden, quantified as the sum of additional atherothrombotic risk factors (1, 2, or 3 or more features). Formal interaction testing between risk stratum and DAPT duration was estimated using Cox regression. A p value <0.05 was considered to indicate statistical significance. All data were processed using SPSS version 24.0 (SPSS Inc., Chicago, Illinois) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 3,696 high-risk patients with DM who were event-free at 12 months after index procedure, 2,580 (69.8%) patients received DAPT >1-year, with the mean duration of DAPT was 672 days (SE: 3.31), whereas 1,116 (30.2%) patients received DAPT ≤1-year, of whom the mean duration of DAPT was 349 days (SE: 1.84). The most prevalent enrichment criterion in high-risk patients with DM was multivessel CAD (81.5%), 58.1% had current smoking, 32.1% had age >65 years, 21.9% had previous MI (Figure 2). The prevalence of previous ischemic stroke and chronic renal dysfunction was 12.6% and 5.2%,

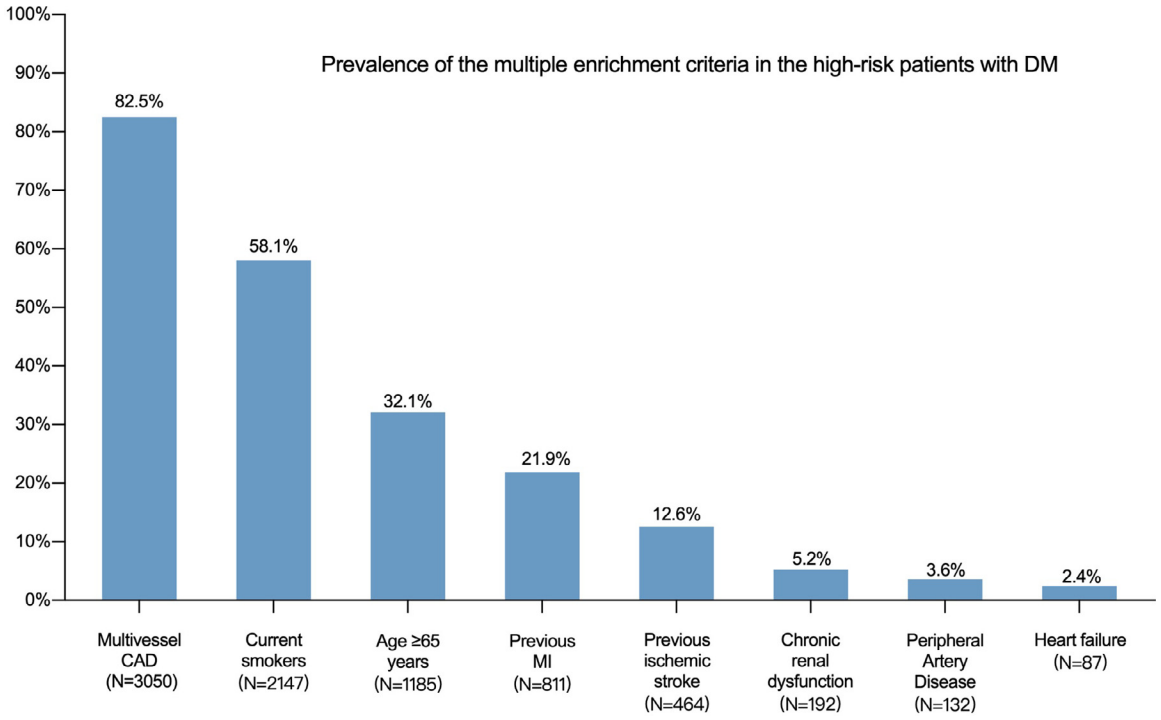


Figure 2. Prevalence of the various enrichment high-risk features in our cohort. Distribution of the prevalence, by range of frequency, of the different enrichment criteria in the high-risk patients with diabetes mellitus.

Table 1
Baseline clinical characteristics in high-risk patients with diabetes mellitus according to DAPT duration

Variable	DAPT >12-month (n = 2,580)	DAPT ≤12-month (n = 1,116)	p Value
Age (y)	59.63 ± 9.88	59.51 ± 9.77	0.735
Men	1923 (74.5%)	856 (76.7%)	0.161
Body mass index, kg/m^2	26.30 ± 3.16	26.30 ± 3.24	0.994
Hypertension	1809 (70.1%)	760 (68.1%)	0.222
Hyperlipidemia	1888 (73.2%)	781 (70.0%)	0.046
Chronic renal dysfunction*	143 (5.5%)	49 (4.4%)	0.147
Current smoker	1,480 (57.4%)	667 (59.8%)	0.174
Heart failure	68 (2.6%)	19 (1.7%)	0.086
Peripheral artery disease	104 (4.0%)	28 (2.5%)	0.022
Previous MI	587 (22.8%)	224 (20.1%)	0.071
Previous PCI	702 (27.2%)	292 (26.2%)	0.511
Previous CABG	130 (5.0%)	53 (4.7%)	0.709
Previous stroke	330 (12.8%)	154 (13.8%)	0.404
Previous major bleeding event	13 (0.5%)	9 (0.8%)	0.272
Anemia	155 (6.0%)	49 (4.4%)	0.050
LVEF (%)	62.42 ± 7.50	62.76 ± 7.20	0.211
Clinical presentation			0.010
Stable ischemic heart disease	1,131 (43.8%)	438 (39.2%)	
Acute coronary syndrome	1,449 (56.2%)	678 (60.8%)	
UA/NSTEMI	1,170 (45.3%)	539 (48.3%)	0.099
STEMI	279 (10.8%)	139 (12.5%)	0.148
Hemoglobin (g/dl)	14.23 ± 1.57	14.23 ± 1.54	0.998
Platelet count (10^9/L)	204.36 ± 55.72	205.97 ± 56.94	0.424
White blood cell count (10^9/L)	6.87 ± 1.69	6.89 ± 1.64	0.697
HbA1c (%)	7.61 ± 1.30	7.50 ± 1.31	0.019
DAPT score	2.13 ± 1.30	2.13 ± 1.28	0.965
PARIS Coronary Thrombotic Events risk score	3.29 ± 1.85	3.29 ± 1.74	0.992
PARIS Major Bleeding risk score	3.82 ± 2.04	3.75 ± 1.91	0.302
PRECISE-DAPT score	11.44 ± 8.61	11.15 ± 8.72	0.355
ARC-HBR	469 (18.2%)	208 (18.6%)	0.740
Medication			
Aspirin	2,551 (98.9%)	1,104 (98.9%)	0.897
Clopidogrel	2,545 (98.6%)	1,103 (98.8%)	0.636
Beta-blocker	2,383 (92.4%)	1,016 (91.0%)	0.174
Calcium channel blockers	1,309 (50.7%)	575 (51.5%)	0.660
Statin	2,479 (96.1%)	1,050 (94.1%)	0.007
Antidiabetic drugs at baseline			
OADs	994 (38.5%)	460 (41.2%)	0.124
Insulin	643 (24.9%)	266 (23.8%)	0.481

Values are mean ± SD or n (%). ACEI = ACE inhibitors; ACS = acute coronary syndrome; ARB = angiotensin receptor blockers; ARC-HBR = Academic Research Consortium-High bleeding risk; CABG = coronary artery bypass grafting. DAPT = dual antiplatelet therapy; HbA1c = glycosylated haemoglobin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; OADs = oral antidiabetes drugs; PCI = percutaneous coronary intervention; PARIS = Patterns of nonadherence to anti-platelet regimen in stented patients; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

* Chronic renal dysfunction = estimated glomerular filtration rate <60 ml/min.

respectively; 3.6% of patients had PAD, and 2.4% had heart failure. Patients with prolonged term (>1-year) had a higher HbA1c values, and more often presented PAD and acute coronary syndrome (ACS) as compared with their counterparts presenting with ≤1-year DAPT duration (Table 1). Multivessel CAD was more frequent and total lesion length was longer in the DAPT >1-year group than the DAPT ≤1-year group (Table 2). After IPTW adjustment, the 2 groups were similar for all available clinical and angiographic characteristics with all absolute standardized differences <10% (Supplementary Table S1).

Follow-up data were available for 99.4% (3,673 of 3,696) of the eligible patients at 24 months after index procedure. After a median follow-up of 29.2 months (IQR: 26.7 to 31.1 months), a total of 91 MACCEs, including 36 all-cause death, 45 stroke, and 21 MIs, were recorded. Results from the multivariable Cox regression analysis showed that DAPT >1-year was associated with 62% lower risk of MACCE than DAPT ≤1-year (1.7% vs 4.1%; adjusted hazard ratio [HR]: 0.382; 95% confidence interval [CI], 0.252 to 0.577; p <0.001; Figure 3, Table 3). The main drivers of MACCE was a significant lower rate of all-cause mortality in the subjects treated with prolonged duration regimen (>1-year) versus short-duration regimen (≤1-year) (0.2% vs 2.9%; adjusted HR: 0.048; 95% CI, 0.017 to 0.135; p <0.001; Figure 3). There were numerically lower rates of MI and stroke with extended DAPT, which did not achieve statistical significance. Adjusted risks of

Table 2
Procedural characteristics in high-risk patients with diabetes mellitus according to DAPT duration

Variable	DAPT >12-month (n = 2,580)	DAPT ≤12-month (n = 1,116)	p Value
Angiographic characteristics			
Multivessel coronary artery disease	2,166 (84.0%)	884 (79.2%)	<0.001
Target vessel			
Left main	85 (3.3%)	28 (2.5%)	0.203
Left anterior descending	2,296 (89.0%)	986 (88.4%)	0.571
Left circumflex	514 (19.9%)	212 (19.0%)	0.515
Right coronary	537 (20.8%)	230 (20.6%)	0.888
Bypass graft	8 (0.3%)	2 (0.2%)	0.482
Target lesion morphology			
Bifurcation lesion	416 (16.1%)	160 (14.3%)	0.169
Chronic total occlusion	224 (8.7%)	81 (7.3%)	0.149
In-stent restenosis	142 (5.5%)	53 (4.7%)	0.346
Severe calcification	105 (4.1%)	38 (3.4%)	0.336
Thrombotic lesion	89 (3.4%)	42 (3.8%)	0.636
Total lesion length (mm)	44.80 ± 28.35	43.02 ± 26.06	0.038
Type B2 or C lesion	2,044 (79.2%)	875 (78.4%)	0.574
SYNTAX score	12.14 ± 8.20	11.58 ± 8.17	0.053
Procedural characteristics			
Arterial access site			0.506
Radial approach	2,338 (90.6%)	1,019 (91.3%)	
Femoral approach	242 (9.4%)	97 (8.7%)	
Use of intravascular ultrasound	142 (5.5%)	55 (4.9%)	0.475
Treated vessels per patient	1.30 ± 0.51	1.28 ± 0.50	0.297
Treated lesions per patient			0.178
1	1,641 (63.6%)	717 (64.2%)	
2	715 (27.7%)	322 (28.9%)	
≥3	224 (8.7%)	77 (6.9%)	
Number of stents implanted per patient	2.01 ± 1.13	1.94 ± 1.04	0.070
≥3 stents implanted	677 (26.2%)	272 (24.4%)	0.233
Total stent length per patient (mm)	44.80 ± 28.35	43.02 ± 26.06	0.073
Total stent length >30 mm	1,556 (60.3%)	664 (59.5%)	0.644
Mean stent diameter (mm)	2.96 ± 0.55	2.98 ± 0.54	0.392
Type of DES implanted			0.865
First-generation DES	266 (10.3%)	113 (10.1%)	
Second-generation DES	2,314 (89.7%)	1,003 (89.9%)	
Glycoprotein IIb/IIIa use	395 (15.3%)	183 (16.4%)	0.403

Values are mean ± SD or n (%). DES = drug-eluting stent; and SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

cardiovascular death (0.1% vs 1.7%; adjusted HR: 0.060; 95% CI, 0.017 to 0.203; p <0.001; Figure 3) and definite/probable ST (0.2% vs 0.6%; adjusted HR: 0.264; 95% CI, 0.083 to 0.845; p = 0.024; Figure 3) were significantly lower in the DAPT >1-year group than the DAPT ≤1-year group. No difference in the primary safety end point of clinically relevant bleeding (1.1% vs 1.2%; adjusted HR: 0.920; 95% CI, 0.467 to 1.816; p = 0.811; Figure 3) was observed with >1-year DAPT compared with ≤1-year DAPT. In an attempt to define net clinical benefit, the risk of the net clinical benefit outcome, comprising all-cause death, stroke, MI, or clinically relevant bleeding was lower with >1-year DAPT compared with ≤1-year DAPT (2.7% vs 5.2%; adjusted HR: 0.471; 95% CI, 0.331 to 0.671; p <0.001; Figure 3).

The results from IPTW adjusted Cox regression analysis were consistent with the main analyses (Table 3). Specifically, patients treated with DAPT >1-year had significantly fewer MACCE (HR_{IPTW}: 0.362 [95% CI, 0.241 to 0.542], p <0.001), cardiovascular mortality (HR_{IPTW}: 0.051 [95% CI, 0.015 to 0.173], p <0.001), and definite/probable ST (HR_{IPTW}: 0.259 [95% CI, 0.083 to 0.806], p = 0.020) compared with ≤1-year DAPT. Clinically relevant bleeding (HR_{IPTW}: 0.969 [95% CI, 0.486 to 1.932]) did not differ significantly between longer than 1-year DAPT group and ≤1-year DAPT group. A lower number of net clinical benefit outcome (HR_{IPTW}: 0.462 [95% CI, 0.327 to 0.652]) was observed in patients treated with DAPT for longer than 1 years.

To assess whether treatment effects differed depending on the number of additional high-risk criteria fulfilled, outcomes were also analyzed comparing longer than 1-year DAPT versus ≤1-year DAPT among subgroups of subjects with 1 (n = 948), 2 (n = 1,540), or 3 or more (n = 1,208) high-risk features in patients with DM. Although the magnitude of the anti-ischemic effect of long-term DAPT versus short-term DAPT regimen tended to be greater as the number of additional high-risk features increased, relative treatment effects were consistent for the outcomes of MACCE, clinically relevant bleeding, and net clinical benefit independent of the accumulation of enrichment criteria, with no significant treatment interactions (all $P_{interaction}$>0.05; Figure 4).

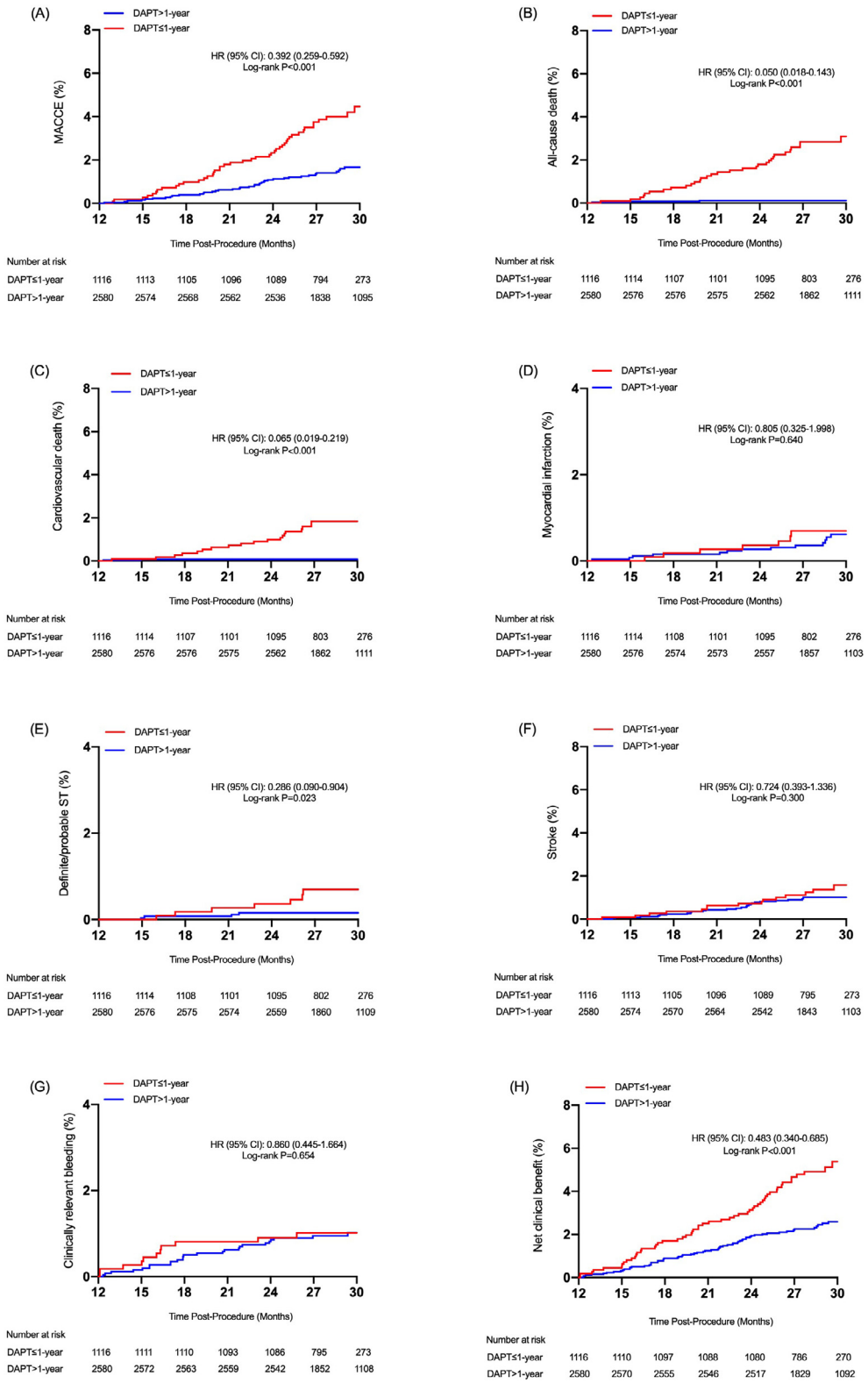


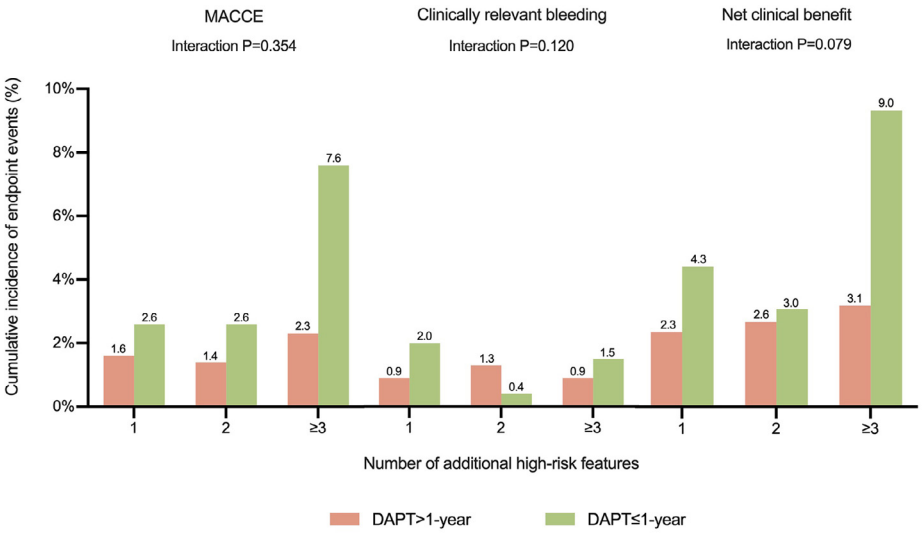
Figure 3. Kaplan-Meier curves for clinical outcomes stratified by DAPT duration. Cumulative incidence of *(A)* major adverse cardiac and cerebrovascular events (MACCE) (composite of all-cause death, myocardial infarction, or stroke); *(B)* all-cause death; *(C)* cardiovascular death; *(D)* myocardial infarction; *(E)* definite/probable stent thrombosis; *(F)* stroke; *(G)* clinically relevant bleeding; and *(H)* net clinical benefit stratified by DAPT duration (>1- versus ≤1-year DAPT). The primary composite major adverse cardiac events (MACCE) end point was defined as the composite of death from any cause, myocardial infarction, or stroke.

Table 3
Comparison of clinical outcomes between >12-month DAPT and ≤12-month DAPT in high-risk diabetic patients

Variable	DAPT >12-month (n = 2,580)	DAPT ≤12-month (n = 1,116)	Univariate Analysis		Multivariable analysis		IPTW analysis	
			HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Major adverse cardiac and cerebrovascular events	45 (1.7%)	46 (4.1%)	0.392 (0.259-0.592)	<0.001	0.382 (0.252-0.577)	<0.001	0.362 (0.241-0.542)	<0.001
Cardiovascular death, myocardial infarction, or ischemic stroke	40 (1.6%)	34 (3.0%)	0.474 (0.300-0.750)	0.001	0.458 (0.289-0.725)	0.001	0.420 (0.270-0.653)	<0.001
All-cause death	4 (0.2%)	32 (2.9%)	0.050 (0.018-0.143)	<0.001	0.048 (0.017-0.135)	<0.001	0.044 (0.015-0.126)	<0.001
Cardiovascular death	3 (0.1%)	19 (1.7%)	0.065 (0.019-0.219)	<0.001	0.060 (0.017-0.203)	<0.001	0.051 (0.015-0.173)	<0.001
Myocardial infarction	14 (0.5%)	7 (0.6%)	0.805 (0.325-1.998)	0.641	0.811 (0.326-2.019)	0.653	0.746 (0.309-1.801)	0.514
Definite/probable stent thrombosis	5 (0.2%)	7 (0.6%)	0.286 (0.090-0.904)	0.033	0.264 (0.083-0.845)	0.025	0.259 (0.083-0.806)	0.020
Stroke	29 (1.1%)	16 (1.4%)	0.724 (0.393-1.336)	0.302	0.705 (0.382-1.303)	0.265	0.726 (0.394-1.340)	0.306
Ischemic stroke	25 (1.0%)	14 (1.3%)	0.716 (0.372-1.381)	0.319	0.692 (0.358-1.335)	0.272	0.701 (0.368-1.338)	0.282
Clinically relevant bleeding	28 (1.1%)	13 (1.2%)	0.860 (0.445-1.664)	0.654	0.920 (0.467-1.816)	0.811	0.969 (0.486-1.932)	0.929
Net clinical benefit	70 (2.7%)	58 (5.2%)	0.483 (0.340-0.685)	<0.001	0.471 (0.331-0.671)	<0.001	0.462 (0.327-0.652)	<0.001

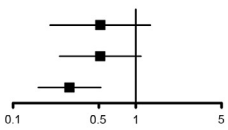
Values are number of events (%) unless otherwise indicated. The covariables included in the multivariable model for ischemic outcomes were age, male sex, acute coronary syndrome, hypertension, previous revascularization (percutaneous coronary intervention and/or coronary artery bypass graft), left ventricular ejection fraction, type of DES implanted, left main or left anterior descending artery involvement, thrombotic lesion, bifurcation lesion, total lesion length, and total number of stents implanted. The covariables included in the model for clinically relevant bleeding were age, male sex, body mass index, acute coronary syndrome, previous major bleeding event, and anemia (hemoglobin <12 g/dl for men and <11 g/dl for women). The covariables included in the model for net clinical benefit outcome were age, male sex, body mass index, acute coronary syndrome, hypertension, previous revascularization, left ventricular ejection fraction, type of DES implanted, left main or left anterior descending artery involvement, thrombotic lesion, bifurcation lesion, total lesion length, total number of stents implanted, previous major bleeding event, and anemia.

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; IPTW = inverse probability of treatment weighting. Other abbreviations as in Table 1 and Table 2.



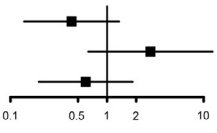
Primary efficacy outcome
(composite of all-cause Mortality, myocardial Infarction, or stroke)

	DAPT>1-year (n=2580)	DAPT≤1-year (n=1116)	HR (95% CI)	P for interaction
Number of high-risk factors				
1 (n=948)	10/644 (1.6%)	8/304 (2.6%)	0.514 (0.201-1.310)	
2 (n=1540)	15/1072 (1.4%)	12/468 (2.6%)	0.513 (0.240-1.099)	0.354
≥3 (n=1208)	20/864 (2.3%)	26/344 (7.6%)	0.288 (0.161-0.517)	



Primary safety outcome
(BARC type 2, 3, or 5 bleeding)

	DAPT>1-year (n=2580)	DAPT≤1-year (n=1116)	HR (95% CI)	P for interaction
Number of high-risk factors				
1 (n=948)	6/644 (0.9%)	6/304 (2.0%)	0.429 (0.138-1.334)	
2 (n=1540)	14/1072 (1.3%)	2/468 (0.4%)	2.809 (0.637-12.388)	0.120
≥3 (n=1208)	8/864 (0.9%)	5/344 (1.5%)	0.601 (0.196-1.843)	



Net adverse clinical events
(all-cause mortality, MI, stroke, and BARC type 2, 3, or 5 bleeding)

	DAPT>1-year (n=2580)	DAPT≤1-year (n=1116)	HR (95% CI)	P for interaction
Number of high-risk factors				
1 (n=948)	15/644 (2.3%)	13/304 (4.3%)	0.476 (0.225-1.005)	
2 (n=1540)	28/1072 (2.6%)	14/468 (3.0%)	0.823 (0.433-1.565)	0.079
≥3 (n=1208)	27/864 (3.1%)	31/344 (9.0%)	0.325 (0.194-0.545)	

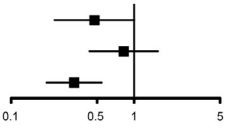


Figure 4. The treatment effect of DAPT >1-year versus DAPT ≤1-year regimen on MACCE, clinically relevant bleeding, and net clinical benefit outcome stratified by number of additional high-risk features fulfilled in patients with DM. The effect of DAPT >1-year versus DAPT ≤1-year for MACCE, clinically relevant bleeding, and net clinical benefit outcome was consistent across subjects with 1 (n = 948), 2 (n = 1,540), or 3 or more (n = 1,208) high-risk risk factors fulfilled in patients with DM with no evidence of effect modification. CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiovascular or cerebrovascular events.

Discussion

In this large-sized contemporary cohort of high-risk patients with DM who underwent PCI, we evaluated the effectiveness and safety of extended duration (>1-year) DAPT against a short course of DAPT (≤1-year). The major findings of the present study were that (1) a vast majority of diabetic patients undergoing PCI with DES had additional atherothrombotic risk factor at baseline; (2) In this high-risk population, prolonged term (>1-year) DAPT resulted in fewer net clinical benefit outcomes primarily by preventing adverse efficacy events, particularly cardiovascular death, whereas clinically relevant bleeding events were less frequent, compared with short-term (≤1-year) DAPT; (3) The beneficial effect of extended DAPT on primary efficacy end point was consistent across the number of enrichment high-risk criteria fulfilled without any significant interaction, with absolute risk reductions that appeared larger in DM patients with accumulated ≥3 additional high-risk characteristics. In aggregate, our data may hence help clinicians in their decision-making process of choosing the optimal DAPT duration in high-risk diabetic patients who are carefully assessed to be at high risk of thrombosis and low risk of bleeding.

In light of each patient's clinical characteristic and circumstance, the optimum duration of DAPT with the scope of minimizing the risk of thrombotic and hemorrhagic events is still a matter of debate.[2] Current American and European guidelines recommend 12-month DAPT duration for patients with ACS, and 6 months for those with stable CAD.[1,12] To date, there is no specific indication for DAPT duration in patients with DM. Historically, observational studies have suggested that abbreviated duration of DAPT could be safe and effective in diabetic patients with either stable CAD or low-risk ACS after coronary second-generation DES placement.[13–15] However, these results might not apply to high-risk patients with DM. Since co-morbidities associated with DM are important contributors to increased ischemic risk and approximately 80% of diabetic patients had at least one additional risk factor,[16] there is a need to define the most DAPT duration options for secondary prevention of atherothrombotic recurrences in high-risk patients with DM.

In the present study, the rate of DAPT discontinuation (30.2%) within 1 year was less frequent in high-risk DM patients, consistent with previous findings by Faggioni et al,[17] in whose study patients with DM had a lower cumulative incidence of DAPT cessation (17.7%) at 1 year. In the EPICOR Asia study, 88.3% and 60.0% of diabetic patients remained on DAPT use at 1 year and 2 years follow-up, respectively.[18] Accumulating evidence has shown that DM was an independent predictor of uninterrupted DAPT after PCI,[19] a fact that the presence of DM might identify patients who benefit from prolonged DAPT. Our results, in concert with those of earlier studies, highlighted that in a real-world practice, physicians are more likely to continue DAPT use after 12 months for high-risk patients with DM, a behavior that might reflect concerns surrounding recurrent atherothrombotic events in such high-risk patients. Currently, controversy exists regarding the optimal DAPT duration to balance the ischemic and bleeding risks in patients with DM, with somewhat inconsistent and contradictory results.[20–23] We extended these earlier observations to a contemporary PCI cohort of high-risk DM patients by elucidating that prolonged DAPT beyond 1 year reduced the excessive risk of ischemic events without a trade-off in bleeding, thereby achieving an increased net clinical benefit, as compared with stopping DAPT ≤1 year. Results from previous observational studies, for instance, suggested that longer duration of DAPT use was associated with a lower incidence of ischemic end points in diabetic patients,[20–22] which was aligned with our overall results. Analogously, the dedicated subanalysis of the DAPT trial showed that continued clopidogrel plus aspirin for 30 months (vs 12 months) reduced the risk of MI in DM patients.[23] In contrast, in a pooled analysis comprising 6 randomized controlled trials (RCT) of participants with DM, long-term compared with short-term DAPT did not prevented ischemic or composite outcomes but slightly increased the risk of bleeding.[24]

These discrepancies may reflect heterogeneity in patient populations, the underlying risks for bleeding, and background pharmacotherapy. First, relatively low-risk nature of the diabetic patients undergoing PCI from previous RCTs precluded conclusive inference regarding the cardiovascular benefits and risks of extended DAPT. Conversely, our high-risk DM patient's cohort have substantially higher risk than the populations enrolled in most RCTs, with at least one additional atherothrombotic risk factor, in turn contributing to high rates of patients with multivessel CAD (82.5%), current smoking (58.1%), previous MI (21.9%), and other co-morbidities. In addition, an analysis from the PROSPECT study showed that the main driver of long-term atherothrombotic events in high-risk DM patients was not events arising from the treated culprit lesions, but rather from new lesions (>50%) originating from medically treated nonculprit lesions.[25] Thus, it is plausible that the later-phase cardiovascular benefit of long-term DAPT in our findings might be driven predominately by reducing de novo atherothrombotic ischemic events. Second, we elected to focus on high-risk patients with DM after PCI who have tolerated 1 year of DAPT, have high ischemic risk, and low bleeding risk. In this regard, we reasoned that these patients would be expected to derive a more favorable benefit-to-risk profile when treated with DAPT continuation beyond 1 year. Third, most studies conducted in East Asian countries consistently identified safety concerns regarding bleeding complications of ticagrelor or prasugrel in East Asian patients after PCI.[26,27] Considering that East Asian patients are considered to be more susceptible to bleeding events,[28] all patients in our cohort treated with clopidogrel could experience the expected benefit of a low rate of bleeding events, lower cost, and potentially comparable ischemic risk compared with potent $P2Y_{12}$ inhibitors. Indeed, a prespecified analysis of PEGASUS-TIMI 54 trial showed that there was an increase in major bleeding with long-term DAPT with ticagrelor and aspirin in patients with DM who had previous MI, although with significant reduction in ischemic cardiovascular events.[29] The THEMIS-PCI trial demonstrated that in patients with DM, stable CAD, and previous PCI, long-term therapy with ticagrelor in addition to aspirin had a lower incidence of ischemic cardiovascular

events but a higher incidence of major bleeding compared with aspirin alone.[30] Further investigations are necessary to evaluate the relative safety and effectiveness of extended DAPT with ticagrelor plus aspirin in East Asian diabetic patients undergoing PCI who are at high ischemic risk and low bleeding risk. Taken together, the present findings are consistent with emerging concept highlighting the importance of DM as an independent correlate of ischemic, but not bleeding, events after PCI,[18] thereby reinforcing the need for intensified antiplatelet therapy in such high-risk patients.

Some limitations of this study should be acknowledged. First, DAPT duration was not randomized, and the observational nature of the Fuwai PCI registry precludes causal inferences. Although we tried to reduce bias to a minimum by multivariable Cox regression and IPTW-adjusted analysis, we cannot exclude unmeasured confounders deriving both from patients and operators' decision. Second, the present analysis might be underpowered due to inadequate sample size and low event rates. Hence, our results warrant cautious interpretation as a type II error is possible. Third, potent $P2Y_{12}$ agents were not prescribed in patients given that the enrollment of this registry was performed before the availability of ticagrelor or prasugrel in China, which otherwise might influence the outcome of this study. Ultimately, we did not collect serum glucose levels nor have other measures of DM severity or its medical control to better characterize patients with DM.

In the large, prospective observational study of DES-treated high-risk DM patients with additional atherothrombotic risk factors, physicians are more likely to recommend remaining on DAPT after 1 year in high-risk DM patients, likely reflecting concerns surrounding cessation of DAPT in the setting of a prothrombotic state. Continuation of DAPT beyond 1 year had lower risks of atherothrombotic events versus short-term (≤1-year) DAPT with similar risks of bleeding events, thereby maximizing a significant net clinical benefit. These observations suggest that extended DAPT might be a viable treatment option in high-risk DM patients with acceptable bleeding risk.

Author Contributions

Hao-Yu Wang: Conceptualization, data curation, formal analysis, investigation, methodology, writing − original draft, writing − review/editing; Zhong-Xing Cai: Conceptualization, data curation, investigation, methodology; Dong Yin: Conceptualization, funding acquisition, writing—review and editing; Yue-Jin Yang: Data curation, investigation; Wei-Hua Song: Investigation, supervision, writing − review/editing; Ke-Fei Dou: Conceptualization, data curation, methodology, supervision, writing—review and editing

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.2020.11.043.

1. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 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;39:213–260.
2. Miyazaki Y, Suwannasom P, Sotomi Y, Abdelghani M, Tummala K, Katagiri Y, Asano T, Tenekecioglu E, Zeng Y, Cavalcante R, Collet C, Onuma Y, Serruys PW. Single or dual antiplatelet therapy after PCI. *Nat Rev Cardiol* 2017;14:294–303.
3. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *New Eng J Med* 2014;371:2155–2166.
4. Hermiller JB, Krucoff MW, Kereiakes DJ, Windecker S, Steg PG, Yeh RW, Cohen DJ, Cutlip DE, Massaro JM, Hsieh WH, Mauri L. Benefits and risks of extended dual antiplatelet therapy after everolimus-eluting stents. *JACC Cardiovasc Interv* 2016;9:138–147.
5. Cavender MA, Steg PG, Smith SC Jr., Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) registry. *Circulation* 2015;132:923–931.
6. Bhatt DL. Antiplatelet therapy following myocardial infarction in patients with diabetes. *Jama* 2012;308:921–922.
7. Brener SJ. More bad news for patients with diabetes and a thin silver lining. *JACC Cardiovasc Interv* 2017;10:655–657.
8. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791–1800.
9. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–1330.
10. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care* 2019;42:S13–S28.
11. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44–122.
12. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr.. 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;68:1082–1115.

13. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125:505–513.
14. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal safety and efficacy of 3-month dual antiplatelet therapy following endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60:1340–1348.
15. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB 3rd, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr., Nicolela EL Jr., Perin MA, Devito FS, Labrunie A, Salvadori D Jr., Gusmao M, Staico R, Costa JR Jr., de Castro JP, Abizaid AS, Bhatt DL. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;310:2510–2522.
16. Goel R, Cao D, Chandiramani R, Roumeliotis A, Blum M, Bhatt DL, Angiolillo DJ, Ge J, Seth A, Saito S, Krucoff M, Kozuma K, Makkar RM, Bangalore S, Wang L, Koo K, Neumann FJ, Hermiller J, Stefanini G, Valgimigli M, Mehran R. Comparative influence of bleeding and ischemic risk factors on diabetic patients undergoing percutaneous coronary intervention with everolimus-eluting stents. *Catheter Cardiovasc Interv* 2020. https://doi.org/10.1002/ccd.29314. Epub ahead of print.
17. Faggioni M, Baber U, Sartori S, Giustino G, Cohen DJ, Henry TD, Farhan S, Ariti C, Dangas G, Gibson M, Giacoppo D, Krucoff MW, Aquino M, Chandrasekhar J, Moliterno DJ, Colombo A, Vogel B, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S, Mehran R. Incidence, patterns, and associations between dual-antiplatelet therapy cessation and risk for adverse events among patients with and without diabetes mellitus receiving drug-eluting stents: results from the PARIS registry. *JACC Cardiovasc Interv* 2017;10:645–654.
18. Guan S, Xu X, Li Y, Li J, Guan M, Wang X, Jing Q, Huo Y, Han Y. Impact of diabetes mellitus on antithrombotic management patterns and long-term clinical outcomes in patients with acute coronary syndrome: insights from the EPICOR Asia study. J Am Heart Assoc 2020:e013476.
19. Kovacic JC, Lee P, Karajgikar R, Baber U, Narechania B, Suleman J, Moreno PR, Sharma SK, Kini AS. Safety of temporary and permanent suspension of antiplatelet therapy after drug eluting stent implantation in contemporary "real-world" practice. *J Interv Cardiol* 2012;25:482–492.
20. Li J, Li Y, Qiu M, Li Z, Yang J, Wang X, Bao D, Wang X, Han Y. Impact of dual antiplatelet therapy duration on 1-year clinical outcomes in diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention: insights from the real-world OPT-CAD study. *Catheter Cardiovasc Interv* 2020;95(Suppl 1):579–586.
21. Cho SW, Park K, Ahn JH, Park TK, Lee SY, Kim J, Lee JM, Yang JH, Song YB, Choi JH, Choi SH, Gwon HC, Lee SH, Ahn J, Carriere KC, Hahn JY. Extended clopidogrel therapy beyond 12 months and long-term outcomes in patients with diabetes mellitus receiving coronary arterial second-generation drug-eluting stents. *Am J Cardiol* 2018;122:705–711.
22. Thukkani AK, Agrawal K, Prince L, Smoot KJ, Dufour AB, Cho K, Gagnon DR, Sokolovskaya G, Ly S, Temiyasathit S, Faxon DP, Gaziano JM, Kinlay S. Long-term outcomes in patients with diabetes mellitus related to prolonging clopidogrel more than 12 months after coronary stenting. *J Am Coll Cardiol* 2015;66:1091–1101.
23. Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip DE, Yeh RW, Garratt KN, Lee DP, Steg PG, Weaver WD, Holmes DR Jr., Brindis RG, Trebacz J, Massaro JM, Hsieh WH, Mauri L. Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized dual antiplatelet therapy study. *Circulation* 2016;133:1772–1782.
24. Gargiulo G, Windecker S, da Costa BR, Feres F, Hong MK, Gilard M, Kim HS, Colombo A, Bhatt DL, Kim BK, Morice MC, Park KW, Chieffo A, Palmerini T, Stone GW, Valgimigli M. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. *BMJ* 2016;355:i5483.
25. Kedhi E, Kennedy MW, Maehara A, Lansky AJ, McAndrew TC, Marso SP, De Bruyne B, Serruys PW, Stone GW. Impact of TCFA on unanticipated ischemic events in medically treated diabetes mellitus: insights from the PROSPECT study. *JACC Cardiovasc Imaging* 2017;10:451–458.
26. Park DW, Kwon O, Jang JS, Yun SC, Park H, Kang DY, Ahn JM, Lee PH, Lee SW, Park SW, Choi SW, Lee SG, Yoon HJ, Ahn T, Kim MH, Nah DY, Lee SY, Chae JK, Park SJ. Clinically significant bleeding with Ticagrelor versus Clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. *Circulation* 2019;140:1865–1877.
27. Numasawa Y, Sawano M, Fukuoka R, Ejiri K, Kuno T, Shoji S, Kohsaka S. Antithrombotic strategy for patients with acute coronary syndrome: a perspective from east asia. *J Clin Med* 2020;9:1963. https://doi.org/10.3390/jcm9061963.
28. Kang J, Park KW, Palmerini T, Stone GW, Lee MS, Colombo A, Chieffo A, Feres F, Abizaid A, Bhatt DL, Valgimigli M, Hong MK, Jang Y, Gilard M, Morice MC, Park DW, Park SJ, Jeong YH, Park J, Koo BK, Kim HS. Racial differences in ischaemia/bleeding risk trade-off during anti-platelet therapy: individual patient level landmark meta-analysis from seven RCTs. *Thromb Haemost* 2019;119:149–162.
29. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, Im K, Murphy SA, Held P, Braunwald E, Sabatine MS, Steg PG. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;67:2732–2740.
30. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstråle W, Chen J, Song Y, Diaz R, Goto S, James SK, Ray KK, Parkhomenko AN, Kosiborod MN, McGuire DK, Harrington RA. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet (London, England)* 2019;394:1169–1180.