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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

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ABSTRACT

OBJECTIVES The aim of this study was to examine the frequency and clinical impact of different cessation patterns of dual-antiplatelet therapy (DAPT) after percutaneous coronary intervention with drug-eluting stents among patients with and those without diabetes mellitus (DM).

BACKGROUND Early DAPT suspension after percutaneous coronary intervention increases the risk for major adverse cardiac events. However, temporal variability in risk and relation to DAPT cessation patterns among patients with DM remain unclear.

METHODS Using data from the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry, 1,430 patients with DM (34%) and 2,777 without DM (66%) treated with drug-eluting stents were identified. DAPT cessation modes were classified as temporary interruption (<14 days), disruption because of bleeding or poor compliance, and physician-recommended discontinuation.

RESULTS During 2-year follow-up, DM was associated with an increased risk for thrombotic events but a similar risk for bleeding. The cumulative incidence of DAPT cessation was significantly lower in patients with versus those without DM (50.1% vs. 55.4%; $p < 0.01$), driven largely by less frequent physician-guided discontinuation beyond 1 year. In contrast, 2-year rates of interruption and disruption were similar between groups. When DAPT was interrupted or discontinued under physician guidance, the risk for major adverse cardiac events was unchanged compared with patients with DM on uninterrupted DAPT. Conversely, when DAPT was disrupted, the risk for major adverse cardiac events increased compared with uninterrupted DAPT, regardless of diabetic status, with no evidence of statistical interaction.

CONCLUSIONS DAPT cessation patterns vary according to diabetic status, with less frequent physician-guided discontinuation among patients with DM. The presence of DM does not emerge as a modifier of cardiovascular risk after DAPT cessation. (J Am Coll Cardiol Intv 2017;10:645-54) © 2017 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

DM = diabetes mellitus

HR = hazard ratio

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

Diabetes mellitus (DM) is a major independent risk factor for cardiovascular diseases, including myocardial infarction (MI), heart failure, and stroke. After a successful percutaneous coronary intervention (PCI), the rate of cardiovascular outcomes in patients with DM is significantly higher than in the general population despite strict glycemic control and treatment of concomitant modifiable risk factors such as hypertension and dyslipidemia (1-4). Although the introduction of second-generation drug eluting stents (DES) has reduced the rate of target lesion failure and repeat revascularization in patients with DM, incidence continues to be higher than in patients without DM (5,6).

SEE PAGE 655

Current clinical practice guidelines on the management of patients undergoing PCI recommend 6- to 12-month dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor following DES implantation unless patients are at high risk for bleeding (7). There is no specific indication for DAPT duration in patients with DM. Therefore, the most appropriate DAPT regimen for patients with DM remains a subject of debate. Recent observational studies have suggested that short-term DAPT could be safe and effective in patients with DM with either stable coronary artery disease or low-risk acute coronary syndromes (ACS) after the implantation of second-generation DES (8-10). However, these results might not apply to high-risk patients with DM and ACS or to patients receiving bare-metal stents or first-generation DES.

Cessation of DAPT treatment after PCI in the general population is critical, because it increases the risk for adverse clinical outcomes. In particular, results from the observational PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry have shown that in an all-comers population undergoing PCI, the effect of DAPT cessation on cardiovascular risk depends not only on the time of cessation but also on the underlying cessation mode (11). The effect of early DAPT cessation in real-world patients with DM is unknown. In this study we used data from the PARIS registry to investigate modes of DAPT cessation in patients with DM up to 2 years after PCI with DES compared with patients without DM. Furthermore, we evaluated the effects of different DAPT cessation modes on the risk for cardiovascular adverse events.

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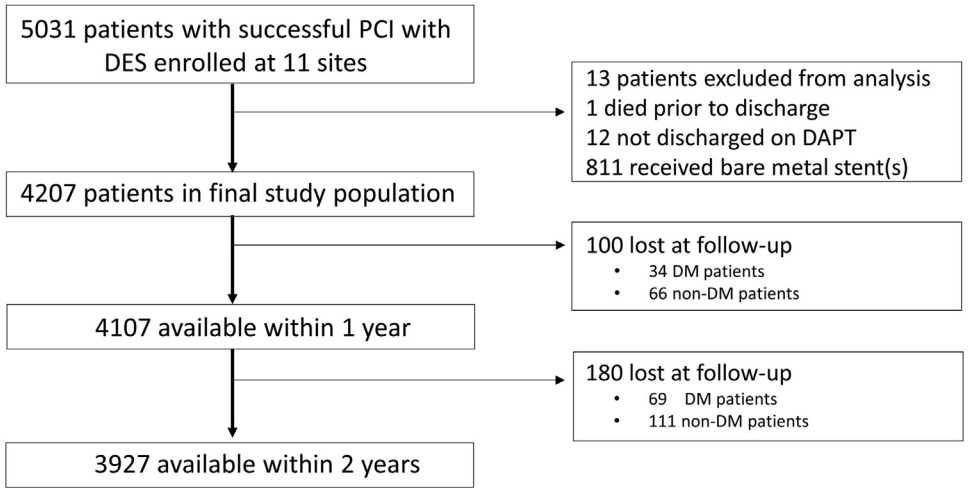
FIGURE 1 Study Flowchart



DAPT = dual-antiplatelet therapy; DES = drug-eluting stent(s); DM = diabetes mellitus; PCI = percutaneous coronary intervention.

METHODS

STUDY POPULATION. PARIS was a multicenter prospective observational study that enrolled patients who were discharged on DAPT after successful PCI with implantation of at least 1 stent between July 2009 and December 2010. The design and results of this study have been previously published (11). Exclusions from the study included PCI for stent thrombosis and participation in an investigational drug or device trial. Patients were followed up via telephone by trained research coordinators at each participating site 1, 6, 12, 24, and 48 months after index PCI to assess DAPT compliance and record any major adverse events. Any relevant source documents were obtained for patients reporting any adverse events. An external clinical events committee adjudicated all events. Among the 5,031 patients enrolled in PARIS, we excluded patients who underwent PCI with 1 or more bare-metal stents. The remaining 4,207 patients constitute the population for this subanalysis and have been divided according to diabetic status. Diabetic status was determined by the presence of a history of DM on the patient's medical record and/or the prescription of glucose-lowering medications. Baseline characteristics, medical treatment, and incidence of DAPT cessation were compared between patients with and those without DM. In addition, we assessed the frequency of any DAPT cessation mode in the 2 groups, patients with and those without DM, and compared the risk for clinical outcomes with any DAPT cessation with uninterrupted DAPT therapy.

STUDY DEFINITIONS. Adverse events were classified as in the PARIS study (11). In brief, the primary major adverse cardiac event (MACE) was defined as a composite of cardiac death, probable or definite stent thrombosis, spontaneous MI, and clinically indicated target lesion revascularization. A more restrictive composite endpoint was also used (MACE 2) that excluded target lesion revascularization. Spontaneous MI was defined as elevated cardiac biomarkers in the presence of clinical or electrocardiographic changes consistent with cardiac ischemia. Stent thrombosis was adjudicated according to the Academic Research Consortium definition (12,13). Target lesion revascularization comprised both percutaneous and surgical reintervention on the target lesion. A bleeding event was defined as one that met the criteria for Bleeding Academic Research Consortium type 3 or greater. All bleeding events were also adjudicated with the TIMI (Thrombolysis In Myocardial Infarction) and ACUITY (Acuity Catheterization and Urgent Intervention Triage Strategy) definitions as a supplement to the Bleeding Academic Research Consortium definition (13). All adjudications were performed by an outside committee. As defined in PARIS, modes of DAPT cessation were identified and classified as follows: physician-guided cessation because of the lack of an indication to continue DAPT (discontinuation), temporary (≤14 days) cessation of

TABLE 1 Baseline Characteristics

	No Diabetes (n = 2,777, 66.0%)	Diabetes (n = 1,430, 34.0%)	p Value
Male	2,125 (76.5)	1,010 (70.6)	<0.0001
Age, yrs	63.4 ± 11.5	64.5 ± 10.1	<0.01
BMI, kg/m^2	28.51 ± 5.17	30.85 ± 5.93	<0.0001
Dyslipidemia	2,052 (73.9)	1,216 (85.0)	<0.0001
Hypertension	2,132 (76.8)	1,280 (89.5)	<0.0001
Family history of CAD	882 (31.8)	479 (33.5)	0.25
Ever smoker	1,458 (52.5)	712 (49.8)	0.01
Education level			<0.0001
Advanced university degree	321 (11.6)	106 (7.4)	
Tertiary university degree	791 (28.5)	400 (28.0)	
Secondary school	1,340 (48.3)	714 (49.9)	
Less than secondary school	264 (9.5)	180 (12.6)	
Ischemic history			
Previous CAD	1,360 (49.0)	825 (57.7)	<0.0001
Previous MI	651 (23.4)	393 (27.5)	<0.05
Previous PCI	1,032 (37.2)	629 (44.0)	<0.0001
Previous CABG	359 (12.9)	244 (17.1)	<0.001
Stroke/CVA	77 (2.8)	69 (4.8)	<0.001
PVD	198 (7.1)	136 (9.5)	<0.01
Cardiac status at admission			
Silent ischemia	288 (10.4)	163 (11.4)	0.30
Stable angina	1,365 (49.2)	806 (56.4)	<0.0001
Acute coronary syndrome	1,124 (40.5)	461 (32.2)	<0.0001

Values are n (%) or mean ± SD.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease including myocardial infarction, PCI, and CABG; CVA = cerebrovascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack.

TABLE 2 Procedural Characteristics

	No Diabetes (n = 2,777, 66.0%)	Diabetes (n = 1,430, 34.0%)	p Value
PCI vessel			
Left main	93 (3.3)	49 (3.4)	0.89
LAD	1,345 (48.4)	677 (47.3)	0.50
Proximal LAD	687 (24.7)	311 (21.7)	0.03
LCx	877 (31.6)	446 (31.2)	0.80
RCA	928 (33.4)	490 (34.3)	0.58
Number of vessels treated			0.80
1	2,342 (84.3)	1,211 (84.7)	
2	404 (14.5)	206 (14.4)	
3	31 (1.1)	13 (0.9)	
Bifurcation lesion	372 (13.4)	153 (10.7)	0.01
Chronic total occlusion	114 (4.1)	58 (4.1)	0.90
Thrombotic lesion	223 (8.0)	57 (4.0)	<0.0001
Stent type			0.20
DES, first-generation	432 (15.6)	242 (16.9)	
DES, second-generation	2,345 (84.4)	1,188 (83.1)	
Number of stents implanted			0.40
1	1,483 (53.4)	736 (51.5)	
2	797 (28.7)	437 (30.6)	
>2	497 (17.9)	257 (18.0)	
Total stent length			0.80
≤20 mm	978 (35.2)	498 (34.8)	
>20 mm	1,799 (64.8)	932 (65.2)	
GP inhibitor	353 (12.7)	161 (11.3)	0.20

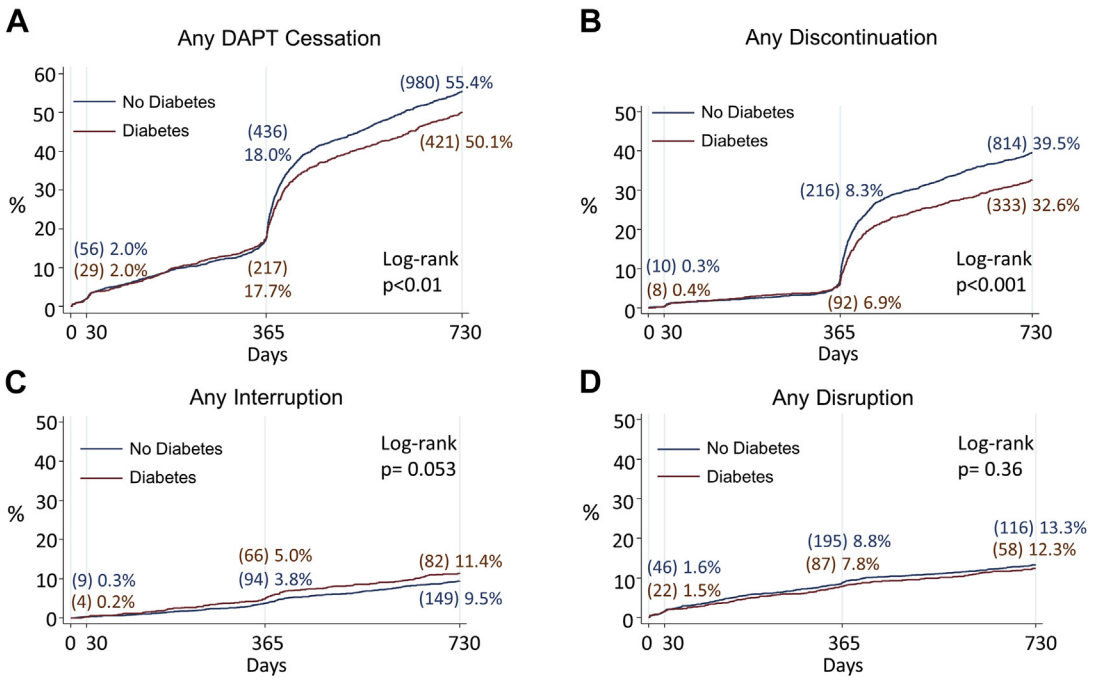
Values are n (%).

DES = drug-eluting stent(s); GP = glycoprotein; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

DAPT because of the need for an invasive procedure (interruption), and DAPT cessation because of a lack of adherence or a bleeding event (disruption). Importantly, DAPT cessation events were not mutually exclusive, and patients could experience more than 1 DAPT cessation mode (discontinuation, interruption, or disruption) during the investigation time. In that case, the DAPT cessation variable was adjudicated according to the following hierarchical order: disruption had priority over interruption, which in turn had priority over recommended discontinuation. Additionally, DAPT cessation longer than 30 days did not preclude the reinclusion of patients subsequently resuming DAPT.

STATISTICAL ANALYSIS. Categorical variables are expressed as percentages and were compared, between patients with and those without DM, using chi-square tests. Continuous variables are expressed as mean ± SD and were compared using Student *t* test. Kaplan-Meier estimates represent time to event incidences and were compared using log-rank tests. Risk for cardiovascular outcomes according to DAPT cessation mode in patients with and those without DM was calculated using an extended Cox regression, a flexible modeling approach that allows departures from proportional hazards with covariates that either interact with or vary by time (14,15). DAPT cessation entered the model as a time-updated categorical variable as previously described (11). Other covariates included in the model were age, sex, body mass index, smoking status, clinical presentation, region (United States vs. Europe), education level, stent type (second vs. first generation), prior MI, prior coronary artery bypass graft surgery, prior PCI, thrombotic lesion, bifurcation lesion, multivessel PCI (1-vessel vs. 2- or 3-vessel PCI). Hazard ratios (HRs) are expressed using uninterrupted DAPT as a comparator within each study group, patients with and those without DM. A test for interaction was performed between diabetic status and DAPT cessation pattern. Stata version 12.1 (StataCorp, College Station, Texas) and SAS version 9.3 (SAS Institute, Cary, North Carolina) were used for the statistical analyses.

FIGURE 2 **Cumulative Incidences of Dual-Antiplatelet Therapy Cessation Across the Follow-Up Time Points, Overall and by Mode**



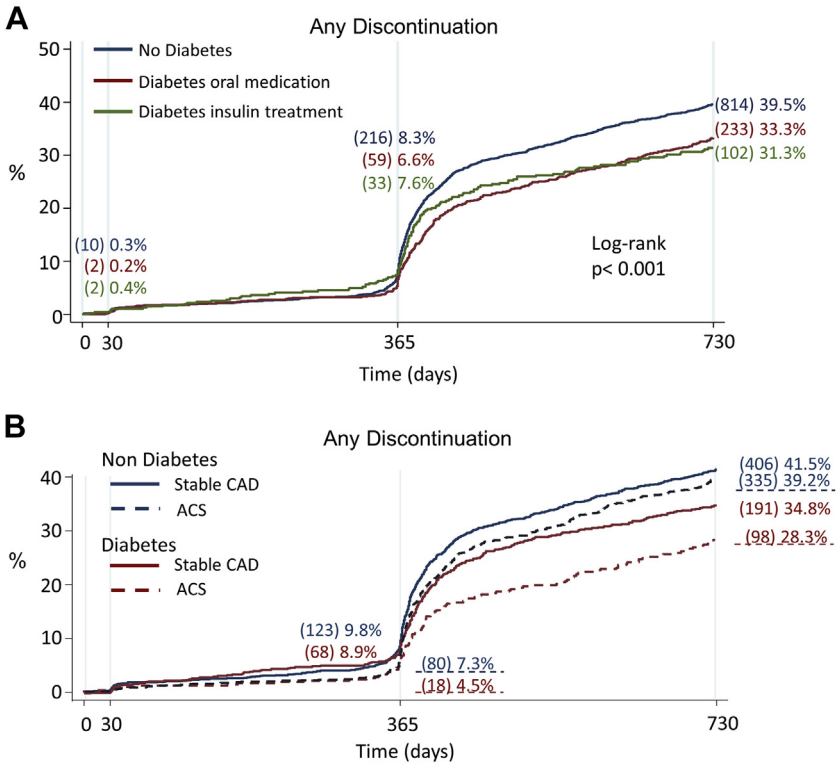
(A) The cumulative incidence of any DAPT cessation through 2 years after PCI in patients with and without diabetes mellitus. The cumulative incidence of DAPT discontinuation, interruption, and disruption are represented in **B, C, and D**, respectively. DAPT = dual-antiplatelet therapy.

RESULTS

BASELINE CHARACTERISTICS. Among the 5,031 patients enrolled in the PARIS registry, 4,207 received at least 1 DES during their index PCI and were included in this subanalysis (see study flowchart in Figure 1). Of this cohort, 1,430 patients (34.0%) had DM. Table 1 shows the baseline characteristics of the study population according to diabetic status. In brief, patients with DM were more often male (70%) and older (63.4 ± 11.5 years vs. 64.5 ± 10.1 years; $p < 0.01$) and had a higher frequency of cardiovascular risk factors such as hypertension and hypercholesterolemia compared with those without DM. However, they were less likely to be current or past smokers. Diabetic status was associated with a history of cardiovascular diseases, including previous MI, previous PCI with stent implantation, coronary artery bypass graft surgery, stroke, and peripheral vessel disease. Upon admission, patients with DM more often presented with silent ischemia or with stable coronary disease. On the contrary, ACS including both non-Q-wave and Q-wave MI were more common among patients without DM.

MEDICATION USE AND ADHERENCE TO DAPT. At the time of admission, patients with DM were significantly more likely to receive aspirin, thienopyridine, and bivalirudin. They were also more often on long-term oral anticoagulant therapy. The use of low-molecular weight heparin and glycoprotein IIb/IIIa inhibitors was similar between the 2 groups (Online Table 1). During the index PCI, proximal left anterior descending coronary artery disease, bifurcation lesions, and thrombotic lesions were more common among patients without DM. There was no significant difference between patients with and those without DM in terms of number of treated vessels, number of stents implanted, and total stent length. Second-generation DES were preferred in patients with DM (83.1% second generation vs. 16.9% first generation) (Table 2). The rate of any DAPT cessation at 30 days was similar between patients with and those without DM (2% vs. 2%; p = NS). However, at 1 and 2 years after index PCI, patients with DM had a lower DAPT cessation rate compared with those without DM (17.7% vs. 18.0% at 1 year and 50.1% vs. 55.4% at 2 years; $p < 0.01$) (Figure 2).

FIGURE 3 Cumulative Incidences of Dual-Antiplatelet Therapy Discontinuation on the Basis of Antidiabetic Treatment and Clinical Presentation



(A) Cumulative DAPT discontinuation rate in nondiabetics, diabetics on oral glucose lowering medications, and diabetics on insulin treatment; **(B)** cumulative DAPT discontinuation rate by clinical presentation, stable CAD or ACS, in nondiabetics and diabetics. ACS = acute coronary syndrome(s); CAD = coronary artery disease.

When distinguishing between modes of cessation, physician-guided discontinuation was less common in patients with DM through 2 years (32.6% of overall DM vs. 39.5% of all patients without DM; $p < 0.001$). There was no significant difference in either DAPT interruption or DAPT disruption between groups, although interruption tended to be more frequent in patients with DM at 1 and 2 years after index PCI (5.0% vs. 3.8% at 1 year and 11.4% vs. 9.5% at 2 years; $p = 0.053$) (Figure 2). Because DAPT discontinuation emerged as the only cessation mode to differ between the study groups, next, we investigated patterns of DAPT discontinuation in relevant subsets of the study population. We found no difference in the pattern of DAPT discontinuation according to antidiabetic treatment, oral medication or insulin (Figure 3A). However, a subanalysis by clinical presentation showed a lower rate of DAPT discontinuation at any time point in patients presenting with ACS compared with stable CAD counterparts in both patients with and those without DM. Interestingly, the difference in the incidence of discontinuation at 2 years between those presenting with stable CAD and those with ACS was 3 times higher in patients with DM than in those without DM (Figure 3B).

CLINICAL OUTCOMES. At 2 years after index PCI, patients with DM had significantly higher rates of all-cause mortality (5.9% vs. 2.3%; $p < 0.0001$), cardiac mortality (4.3% vs. 1.5%; $p < 0.0001$), probable or definite stent thrombosis (1.7% vs. 0.9%; $p = 0.02$), clinically indicated target lesion revascularization (8.5% vs. 5.6%; $p < 0.001$), spontaneous MI (5.0% vs. 2.3%; $p < 0.0001$), and MACE (13.8% vs. 8.2%; $p < 0.0001$) than patients without DM (Table 3). Results were consistent over time at both 1 and 2 years, whereas at 30 days after index PCI, only all-cause mortality and cardiac death were significantly higher among patients with DM (data not shown). There was no difference in bleeding rates during the 2 years of follow-up according to TIMI and Bleeding Academic Research Consortium criteria (Table 3).

When analyzed by antidiabetic treatment, we found that the risk for MACE, MACE 2, cardiac death, and MI was uniform in the diabetic population regardless of treatment (Online Figure 1). Finally, we looked at the time-adjusted risk for cardiovascular events across DAPT cessation patterns compared with uninterrupted DAPT and observed that patients with DM had a higher risk for all ischemic outcomes only during disruption (MACE at disruption: HR: 2.05 [95% confidence interval (CI): 1.27 to 3.30]; $p < 0.001$; MACE 2 at disruption: HR: 2.43 [95% CI: 1.39 to 4.23]; $p < 0.001$; MI at disruption: HR: 3.07 [95% CI: 1.50 to 6.23]; $p < 0.001$) (**Figure 4**). Conversely, patients without DM with DAPT disruption had only a higher risk for MI compared with uninterrupted DAPT (MI at disruption: HR: 3.99 [95% CI: 2.10 to 7.57]; $p < 0.001$), which resulted in a significantly higher rate of MACE 2 (HR: 2.24; 95% CI: 1.28 to 3.92; $p < 0.001$). Interestingly, physician-recommended DAPT discontinuation and interruption for ≤14 days were safe in both patients with and those without DM (MACE at interruption in patients with DM: HR: 1.75 [95% CI: 0.92 to 3.31]; $p = 0.08$; MACE at interruption in patients without DM: HR: 1.32 [95% CI: 0.66 to 2.64]; $p = 0.40$). There was no interaction between diabetic status and clinical outcomes for any cessation mode (**Figure 4**). When patients with DM were subdivided by antidiabetic treatment, we observed that disruption significantly increased the risk for MACE in patients with DM treated with insulin but not with oral medication (Online Figure 2). However, because of the limited number of adverse events in treatment-based subgroups, these results should be interpreted with caution.

TABLE 3 Rate of Clinical Outcomes at 12 and 24 Months

	No Diabetes (n = 2,777)	Diabetes (n = 1,430)	p Value
Death			
12 months	25 (0.90)	46 (3.22)	<0.0001
24 months	65 (2.34)	84 (5.87)	<0.0001
Cardiac death			
12 months	19 (0.68)	37 (2.59)	<0.0001
24 months	41 (1.48)	62 (4.34)	<0.0001
Probable/definite stent thrombosis			
12 months	18 (0.65)	22 (1.54)	<0.01
24 months	25 (0.90)	25 (1.75)	0.02
Target lesion revascularization			
12 months	109 (3.93)	77 (5.38)	0.03
24 months	157 (5.65)	121 (8.46)	<0.001
Myocardial infarction			
12 months	33 (1.19)	46 (3.22)	<0.0001
24 months	63 (2.27)	71 (4.97)	<0.0001
TIMI major			
12 months	37 (1.33)	20 (1.40)	0.86
24 months	52 (1.87)	26 (1.82)	0.90
BARC major			
12 months	61 (2.20)	42 (2.94)	0.14
24 months	92 (3.31)	57 (3.99)	0.26
MACE			
12 months	142 (5.11)	121 (8.46)	<0.0001
24 months	227 (8.17)	197 (13.78)	<0.0001
MACE 2			
12 months	57 (2.05)	80 (5.59)	<0.0001
24 months	105 (3.78)	127 (8.88)	<0.0001

Values are n (%).

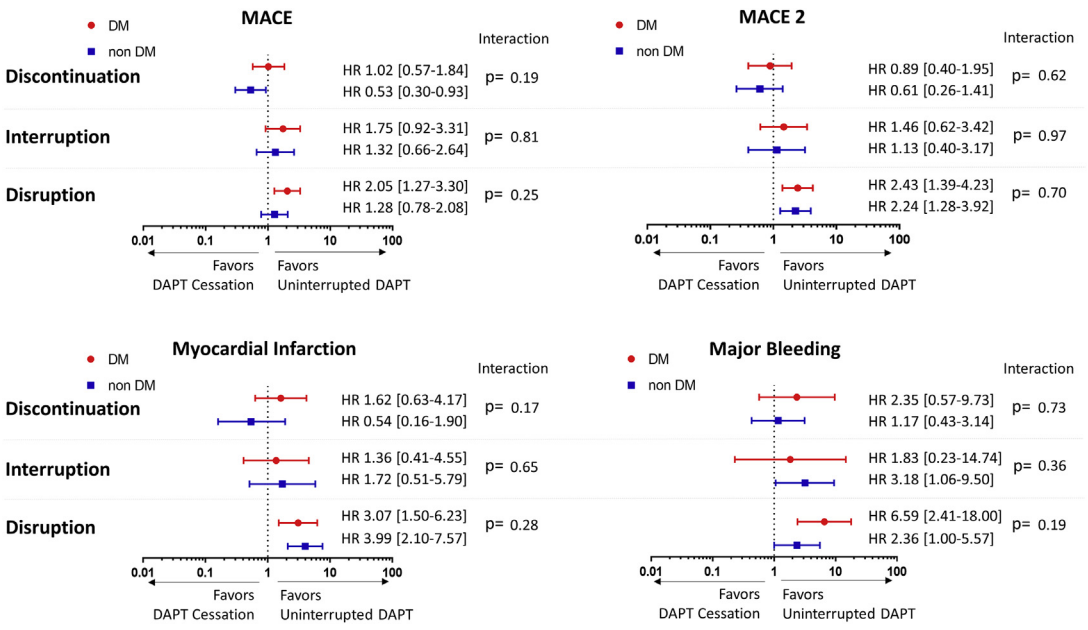
BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiac event(s) (cardiac death, myocardial infarction, clinically indicated target lesion revascularization, or definite or probable stent thrombosis); MACE 2 = major adverse cardiac event(s) 2 (cardiac death, myocardial infarction, or definite or probable stent thrombosis); TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

In the present analysis involving more than 4,000 real-world patients undergoing PCI predominantly with second-generation DES, we report the following key findings: 1) the presence of DM was associated with increased thrombotic but not bleeding events over 2 years; 2) DAPT cessation was less frequent among patients with DM, which was attributable primarily to differences in rates of physician-guided discontinuation between groups; 3) cardiovascular risk after DAPT cessation because of physician-recommended discontinuation or temporary interruption was not increased among patients with versus without DM; and 4) conversely, when DAPT was disrupted because of bleeding or noncompliance, the risk for all cardiovascular adverse events significantly increased in a uniform manner irrespective of diabetic status. In aggregate, these findings suggest that physicians are reluctant to recommend discontinuation of antiplatelet therapy among patients with DM, a practice pattern that is concordant with the prothrombotic nature of such patients. We also demonstrate that DM is not a modifier of risk subsequent to DAPT cessation irrespective of underlying mode.

Overall, the cumulative rate of DAPT cessation was lower among patients with DM, a finding that was driven primarily by differences in the rates of physician-recommended discontinuation. In contrast, the incidence of temporary DAPT interruption did not differ significantly between groups. Previous studies have shown that DM is an independent predictor of uninterrupted DAPT after PCI, together with unstable presentation, prior MI, left main coronary PCI, and multivessel coronary disease (16,17). Our results extend these earlier observations by suggesting that in a real-world context, physicians are less likely to stop DAPT among those with DM, a behavior that might reflect concerns surrounding

FIGURE 4 Adjusted Risk for Adverse Cardiac Events at 2 Years According to Dual-Antiplatelet Therapy Cessation Mode in Patients With and Without Diabetes Mellitus



Patients on dual-antiplatelet therapy (DAPT) were used as the reference. All models included the following variables: age, sex, body mass index, smoking habit, clinical presentation, region, education level, stent type, prior myocardial infarction, prior coronary artery bypass grafting, prior percutaneous coronary intervention (PCI), thrombotic lesion, bifurcation lesion, and multivessel PCI. DM = diabetes mellitus; HR = hazard ratio with 95% confidence interval; MACE = major adverse cardiac event(s) (cardiac death, myocardial infarction, clinically indicated target lesion revascularization, or definite or probable stent thrombosis); MACE 2 = major adverse cardiac event(s) 2 (cardiac death, myocardial infarction, or definite or probable stent thrombosis).

coronary thrombosis and stent thrombosis in such patients. This practice pattern is consistent with emerging risk algorithms highlighting the importance of DM as an independent correlate of thrombotic, but not bleeding, events after PCI, thereby reinforcing the need for longer or more potent platelet inhibition in such patients (18,19). Results from a subanalysis of the DAPT trial, for example, suggest that prolonging DAPT might reduce the risk for outcomes in patients with DM, whereas the benefit appears to be attenuated compared with those without DM (20). In contrast, other data from clinical trials suggest the opposite. In a subanalysis of the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial, 3 months of DAPT duration was noninferior to 12 months in reducing the rate of net adverse clinical and cerebral events and major cardiovascular events in a diabetic subgroup treated with second-generation zotarolimus-eluting stents (8). Similarly, a substudy of the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial found no benefit in prolonging DAPT over 6 months in patients with DM after the implantation of any second-generation DES (21). Whether these differences reflect heterogeneity in patient populations, stent platforms, or study design remains unknown. Although our results provide insight into clinical decision making vis-à-vis DAPT cessation in the setting of DM, we are unable to comment on the optimal DAPT strategy in such patients given the observational nature of our study design. Clearly, additional investigation is warranted to further refine the risk/benefit trade-off with different DAPT durations in patients with DM. Interestingly, we observed no clear difference in the discontinuation pattern on the basis of antidiabetic treatment.

In contrast to our findings with respect to physician-guided discontinuation, we observed no differences between groups in rates of temporary interruption because of surgical procedures or disruption arising from bleeding or noncompliance.

These results suggest that the presence of DM does not play a significant role in clinical decision making with respect to suspension of antiplatelet therapy when prompted by external conditions, such as bleeding. As rates of bleeding were similar between patients with and those without DM, the lack of any differences in disruption is somewhat expected. However, the comparable rates of interruption between groups may be less intuitive given the well-established links between DM and increased platelet reactivity, coupled with the procoagulant milieu that characterizes the post-operative state (22,23). Several reasons might account for the lack of a significant association between DM and propensity to interrupt at time of surgery. First, most instances of interruption involved withdrawal of a single antiplatelet agent, whereas thrombotic risk in this setting is usually related to cessation of both drugs (24). Second, brief episodes of interruption may confer less risk in the setting of relatively safe second-generation DES compared with earlier stent platforms. Third, short-term bleeding risk at the time of surgery may outweigh comparable risks for thrombosis upon withdrawal of antiplatelet therapy, even in the setting of DM.

STUDY LIMITATIONS. PARIS is a prospective registry, and all information on DAPT compliance was self-reported and therefore subject to potential bias. To simplify the statistical analysis, similarly to the main PARIS study, duration of DAPT cessation (brief, temporary, or permanent) was not taken into account in the time-dependent multivariate regression analysis. Risk for cardiovascular outcomes for every DAPT cessation mode was not classified according to the drug type stopped (aspirin, $P2Y_{12}$ inhibitor, or both). In addition, in the PARIS registry only 6% of patients were prescribed a novel $P2Y_{12}$ inhibitor (prasugrel), so comparison between different thienopyridines cannot be performed. Because of the limited number of events and subgroup nature of this analysis, we were unable to examine temporal variability in risk for adverse events associated with each DAPT cessation mode.

CONCLUSIONS

Patients with DM present a higher cardiovascular risk that persists for up to 2 years after index PCI. Clinicians are less likely to recommend discontinuation of DAPT among patients with DM, a behavior that might reflect concerns surrounding cessation of antiplatelet therapy in the setting of a prothrombotic state. Brief episodes of DAPT interruption or physician-recommended discontinuation were not linked to increased risk for adverse events among those with DM. However, disruption for poor compliance or bleeding complications was associated with excess cardiovascular risk irrespective of diabetic status.

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PERSPECTIVES

WHAT IS KNOWN? The risk for ischemic events after cessation of DAPT in PCI-treated patients depends not only on the timing but also on the reasons and duration of DAPT cessation. Although it is well known that DM increases the risk for adverse outcomes after PCI, how different DAPT cessation modes occur in patients with DM and their subsequent risk for adverse outcomes is unknown.

WHAT IS NEW? In patients with DM, DAPT cessation within 2 years after PCI is less common than in patients without DM, mostly because of lower rates of physician-recommended discontinuation. DAPT disruption because of bleeding events or noncompliance is the only DAPT cessation mode to increase cardiovascular risk irrespective of diabetic status.

WHAT IS NEXT? New strategies should be developed to reduce the risk for ischemic events after bleeding-induced DAPT disruption.

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KEY WORDS bleeding, compliance, DAPT cessation, diabetes mellitus, dual-antiplatelet therapy

APPENDIX For supplemental figures and a table, please see the online version of this article.