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Impact of Diabetes on Long-Term Outcomes of Percutaneous Coronary Intervention for Coronary Bifurcation Lesions

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ABSTRACT

Background: Diabetes mellitus (DM) is a well-known risk factor for cardiovascular diseases, including coronary artery diseases (CAD). Complex percutaneous coronary intervention (PCI) such as PCI for bifurcation lesions often yields poor outcomes, especially in DM patients.

Aims: The effect of DM on cardiovascular outcomes in bifurcation PCI was investigated in this retrospective, multicenter, observational, real-world registry of 2648 patients with coronary bifurcation lesions undergoing PCI with contemporary drug-eluting stents (DES).

Methods: The primary outcome was target lesion failure (TLF), defined as a composite of cardiac death, target vessel myocardial infarction and target lesion revascularization. The adjusted outcomes were compared using 1:1 propensity score (PS) matching.

Results: Overall, DM patients were more likely to be older, female, and have hypertension or chronic kidney disease. After PS matching, the cumulative incidence of the primary outcome remained higher in the DM group (7.9% vs. 5.5%, log-rank $p = 0.033$). In multivariable analysis, DM (HR, 1.57; 95% CI, 1.02−2.43; $p = 0.040$), chronic kidney disease (HR, 2.62; 95% CI, 1.27−5.38; $p = 0.008$), low left ventricular ejection fraction (HR, 1.92; 95% CI, 1.10−3.35; $p = 0.022$) and the two-stent technique (HR, 2.18; 95% CI, 1.17−4.05; $p = 0.013$) were independent predictors of TLF. For patients with intravascular ultrasound-guided PCI, TLF rates were similar between DM and non-DM groups (9.1% vs. 7.3%, log-rank $p = 0.347$).

Conclusion: For patients with coronary bifurcation lesions undergoing contemporary PCI, 5-year TLF rates were worse in DM patients. Careful planning and usage of imaging devices may help ameliorate outcomes for DM patients.

Abbreviations: COBIS, COronary BIfurcation Stenting registry; DES, drug-eluting stent; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; PSM, propensity score matching; TLF, target lesion failure; TLR, target lesion revascularization.

For a complete list of the COBIS III investigators, see the Acknowledgments section.

1 | Introduction

Diabetes mellitus (DM) is a well-established risk factor for the development of coronary artery diseases and for adverse cardiovascular events thereafter [1, 2]. The generalized prothrombotic state and the impairment of endothelial functions, thus promoting a pro-inflammatory and proatherogenic environment, contribute to worse outcomes after percutaneous coronary interventions (PCI) in diabetic patients [3, 4].

Coronary bifurcation lesions, which are reported to involve up to 10% of all PCI cases, add further complexity to the procedure [5]. Bifurcation sites are anatomically and functionally different to non-bifurcation lesions, comprising of three distinct segments of proximal main vessel (MV), distal MV and side branch (SB). This puts bifurcation lesions at an elevated risk of endothelial dysfunction due to higher endothelial shear stress, which may initiate or worsen plaque progression [5]. In a study by Capodanno et al., DM patients showed worse long-term outcomes after bifurcation PCI [6]. Recent advancements in stent technology and medical therapy, however, may allow for better outcomes for contemporary PCI even in diabetic patients.

The present study aimed to investigate the clinical and angiographic outcomes of DM and non-DM patients in coronary bifurcation PCI with contemporary drug-eluting stent (DES), by using a propensity-matched cohort from a large-scale, real-world registry.

2 | Methods

2.1 | Study Design and Study Population

The COBIS (COronary BIfurcation Stenting) III registry is a retrospective, multicenter, observational, real-world registry of 2648 patients with coronary bifurcation lesions who underwent PCI with second-generation DES (NCT03068494). For inclusion in the registry, patients had to be at least 19 years old, and present with any form of coronary bifurcation lesion in a major epicardial artery with an MV diameter of ≥ 2.5 mm, and an SB diameter of ≥ 2.3 mm confirmed by core laboratory quantitative coronary angiography (QCA) analysis and was treated solely with second-generation DES. The major exclusion criteria were cardiogenic shock or cardiopulmonary resuscitation during hospitalization, protected left main (LM) disease, and severe left ventricular systolic dysfunction (LVEF < 30%). The Institutional Review Board of each hospital approved the study protocol and waived the requirement for written informed consent due to the retrospective nature of the study. The study complied with the provisions of the Declaration of Helsinki. The registry was supported by the Korean Bifurcation Club and Korean Society of Interventional Cardiology.

2.2 | PCI Procedure

PCI procedures were conducted in accordance with the standard guidelines. Aspirin and P2Y12 inhibitors were loaded with appropriate doses (aspirin, 300 mg; clopidogrel, 600 mg; ticagrelor, 180 mg; prasugrel, 60 mg) before PCI, unless the patient was already on maintenance dosage of the drug. Aspirin was continued indefinitely after PCI; P2Y12 inhibitors were prescribed as per the physician's medical judgment. The targeted activated clotting time during the procedure was 250−300 s, by low-molecular weight heparin or unfractionated heparin. All treatment strategies including the access site, the stent type, and the use of intravascular imaging devices were left to the physician's discretion.

2.3 | Data Collection and Quantitative Coronary Angiographic Measurements

Baseline clinical characteristics, medications, angiographic data, procedural data and follow-up clinical outcomes were collected and reported on a Web-based system. Patients were contacted by telephone for additional information if necessary. All coronary angiograms were reviewed and analysed quantitatively by an independent core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Korea) using validated software (Centricity CA 1000, GE Healthcare, Wisconsin, USA). Bifurcation lesions were classified according to the Medina classification [7]. In left circumflex or right coronary artery bifurcation lesions, the larger of the 2 branches was defined as the MV. Medina classification type 1.1.1, 1.0.1, and 0.1.1 lesions were defined as true bifurcation lesions. Bifurcation angle, minimum lumen diameter (MLD), reference vessel diameter (RD), and lesion length for each vessel were measured, and percent diameter stenosis (100 x [RD/MLD]/RD]) was calculated for each vessel.

2.4 | Outcomes and Definitions

The primary outcome was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TVMI) and target lesion revascularization (TLR). Secondary outcomes included major adverse cardiac event (MACE), defined as a composite of all-cause death, myocardial infarction (MI) and stroke; cardiac death, stroke, MI, target vessel MI (TVMI), stent thrombosis, target vessel revascularization (TVR) and TLR.

All-cause death was defined as any post-procedure death during follow-up. All mortality cases were considered cardiac in origin unless a definite noncardiac cause could be established. MI was defined as an elevation of creatine kinase-myocardial band or troponin level greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiography findings indicative of ischemia that was not related to the index procedure. Stent thrombosis was defined according to the Academic Research Consortium definition [8]. Both definite and probable cases were recorded as stent thrombosis in this study. TVR was defined as repeat PCI or coronary artery bypass graft (CABG) for the target vessel. TLR was defined as repeat PCI or CABG of the lesion in the previously stented segment or in the adjacent 5 mm.

2.5 | Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median (interquartile range [IQR]) and categorical variables

are reported as numbers and percentages. Comparisons of continuous variables were done using Student's *t*-test or Wilcoxon's rank-sum test, and categorical variables were compared using the chi-square test or the Fisher exact test as appropriate. Cumulative-event probabilities were estimated using the Kaplan–Meier method for outcomes and were compared using the log-rank test. Multivariable regression analysis was conducted using Cox proportional hazards model and was used to identify predictors of MACE. In the multivariable analysis, variables with $p < 0.20$ in the univariable analyses or which are clinically relevant were included, which were as follows: old age (> 75 years), sex, DM, hypertension, current smoking status, dyslipidemia, chronic kidney disease (CKD), presentation as acute coronary syndrome (ACS), left ventricular ejection fraction (LVEF) < 50%, LDL > 100 mg/dL, statin usage, LM disease, the use of IVUS imaging, two-stent technique, the number of stents, and final kissing balloon. All *p* values were 2-sided, and $p < 0.05$ was considered significant. Propensity score (PS) matching analysis was performed, and each patient in the DM group was matched with another in the non-DM group at a 1:1 ratio using the nearest neighbor method, with a caliper width equal to 0.2 of the standard deviation of the logit PS. All statistical analyses were performed using R Statistical Software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

After 1:1 matching, a total of 1742 patients were included in the PS-matched cohort (DM group, $n = 871$; non-DM group, $n = 871$).

3.1 | Baseline Characteristics

At baseline, most demographic features showed statistically significant differences between the DM and non-DM groups. (Table 1) DM patients were older and were more female. Patients with DM were also less likely to be a current smoker and more likely to be diagnosed with hypertension or CKD. A two-stent technique was more commonly used in DM patients (19.5% vs. 15.9%, $p = 0.027$), and relatively fewer number of stents were used in DM patients (1.7 vs. 2.1, $p < 0.001$). The usage of intravascular ultrasound (IVUS) imaging was similar between the DM and non-DM groups (39.4% vs. 40.5%, $p = 0.628$).

In the PS-matched cohort, all clinical characteristics including demographics, comorbidities, medications and laboratory values at baseline were well balanced to an SMD of < 0.15. (Supporting Information S1: Figure 1) There were no differences between the two groups in the bifurcation location, the number of diseased vessels, the usage of two-stent techniques or the number of stents used (Figure 1).

3.2 | DM and Long-Term Clinical Outcomes

In the PS-matched cohort, TLF occurred in 69 (7.9%) patients with DM and 48 (5.5%) patients without DM during a median follow-up of 4.4 years (IQR 3.1−5.7 years), (Table 2) and the difference was statistically significant (log-rank $p = 0.033$). Of the individual components of TLF, cardiac death (3.2% vs. 1.8%, log-rank $p = 0.060$) and TLR (4.9% vs. 3.2%, log-rank $p = 0.051$) were higher in the DM group, with marginal statistical significance. TVMI was not significantly different between the two groups (0.8% vs. 0.9%, log-rank $p = 0.830$). Additionally, under IVUS imaging guidance, the difference between the DM and non-DM groups for TLF occurrence was diminished. (HR, 1.29; 95% CI, 0.76−2.20; log-rank $p = 0.347$) (Supporting Information S1: Figure 2)

The occurrences of MACE, (8.7% vs. 7.5%, log-rank $p = 0.276$), all-cause death (5.5% vs. 3.9%, log-rank $p = 0.090$), TVR (7.5% vs. 5.4%, log-rank $p = 0.056$) and ST (1.3% vs. 0.7%, log-rank $p = 0.221$) were all higher in the DM group but without statistical significance (Table 2).

3.3 | Predictors of MACE

By multivariable analysis in the PS-matched cohort (Table 3 and Figure 2), DM was an independent predictor of TLF (HR, 1.57; 95% confidence interval [CI], 1.02−2.43; $p = 0.040$). CKD (HR, 2.62; 95% CI, 1.27−5.38; $p = 0.008$), LVEF < 50% (HR, 1.92; 95% CI, 1.10−3.35; $p = 0.022$) and the application of a two-stent technique during bifurcation PCI (HR, 2.19; 95% CI, 1.17−4.09; $p = 0.014$) were also associated with an increase in TLF. (Supporting Information S1: Figure 3) The two-stent group had more LM lesions, more true bifurcation lesions, higher presence of multi-vessel disease and longer MV/SB lesion lengths compared with the one-stent group (Supporting Information S1: Table 2).

4 | Discussion

The present study compared the long-term outcomes of bifurcation PCI in patients with and without DM from a large, real-world registry. Our main findings were that (1) after PS matching, TLF occurrence remained higher for the DM group; (2) after PS matching, the difference in MACE occurrence between the DM and non-DM groups was insignificant for up to 5 years; (3) DM, CKD, LVEF < 50% and the two-stent technique were independent predictors of TLF in multivariable analysis; (4) after IVUS-guided PCI, TLF rates were similar in DM and non-DM groups.

DM is present in around 15%−20% of all PCI cases, and bifurcation lesions are present in up to 10% of all PCI cases [9–11]. Guidance on the decision to perform PCI in DM patients in various clinical settings such as acute MI or chronic coronary syndromes are extensively described—mostly that DM patients should be treated based on the same principles as non-DM patients [1, 2]. Traditionally, DM is a known risk factor for adverse outcomes in patients with coronary artery disease, and cardiovascular outcome rates are astutely high for diabetic subgroups in various trials for coronary revascularization [12–15]. However, there are currently no specific recommendations or prognostic perspectives available for bifurcation PCI in DM patients.

In our study, despite efforts to match the DM and non-DM populations for baseline demographics, 5-year TLF remained

TABLE 1 | Baseline and angiographic characteristics of the pre- and post-matched population.

	Pre-PSM DM ($N = 905$)	Non-DM ($N = 1743$)	p value	Post-PSM DM ($N = 871$)	Non-DM ($N = 871$)	p value	SMD
Demographic							
Age	65.3 ± 10.0	62.9 ± 11.4	< 0.001	65.2 ± 10.0	65.7 ± 11.1	0.417	−0.041
Male sex	653 (72.2%)	1360 (78.0%)	0.001	638 (73.2%)	633 (72.7%)	0.829	0.0128
Current smoker	241 (26.6%)	557 (32.0%)	0.005	235 (27.0%)	239 (27.4%)	0.872	−0.0104
Hypertension	592 (65.4%)	912 (52.3%)	0	562 (64.5%)	576 (66.1%)	0.513	−0.0338
Dyslipidemia	362 (40.0%)	647 (37.1%)	0.16	344 (39.5%)	365 (41.9%)	0.329	−0.0492
CKD	72 (8.0%)	31 (1.8%)	0	42 (4.8%)	30 (3.4%)	0.185	0.0509
Clinical presentation			0.007			0.652	0.0074
Stable angina	370 (40.9%)	659 (37.8%)		359 (41.2%)	370 (42.5%)		
NSTE-ACS	458 (50.6%)	867 (49.7%)		437 (50.2%)	419 (48.1%)		
STEMI	77 (8.5%)	217 (12.4%)		75 (8.6%)	82 (9.4%)		
Previous MI	43 (4.8%)	70 (4.0%)	0.432	41 (4.7%)	43 (4.9%)	0.911	−0.0108
Previous PCI	145 (16.0%)	178 (10.2%)	0	136 (15.6%)	138 (15.8%)	0.948	−0.0063
LVEF < 50%	138 (15.2%)	265 (15.2%)	1	131 (15.0%)	121 (13.9%)	0.54	0.0319
LDL	99.5 ± 33.0	108.0 ± 33.6	0	99.9 ± 32.9	99.5 ± 30.6	0.826	0.0102
Creatinine	1.3 ± 1.6	1.0 ± 0.9	0	1.2 ± 1.2	1.1 ± 1.3	0.114	0.0595
hsCRP	1.9 ± 7.3	2.1 ± 9.0	0.62	1.9 ± 7.4	1.6 ± 7.9	0.377	0.0446
Angiograhpic							
Bifurcation location			0.003			0.917	
LM	356 (39.3%)	579 (33.2%)		340 (39.0%)	337 (38.7%)		0.0071
LAD	369 (40.8%)	839 (48.1%)		361 (41.4%)	364 (41.8%)		−0.007
LCX	125 (13.8%)	225 (12.9%)		118 (13.5%)	112 (12.9%)		0.02
RCA	55 (6.1%)	100 (5.7%)		52 (6.0%)	58 (6.7%)		−0.0288
Vessel disease			0.017			0.545	−0.0148
0	8 (0.9%)	28 (1.6%)		8 (0.9%)	14 (1.6%)		
1	784 (45.0%)	361 (39.9%)		356 (40.9%)	344 (39.5%)		
2	346 (38.2%)	620 (35.6%)		326 (37.4%)	322 (37.0%)		
3	190 (21.0%)	311 (17.8%)		181 (20.8%)	191 (21.9%)		
LM disease	217 (24.0%)	361 (20.7%)	0.06	207 (23.8%)	200 (23.0%)	0.734	0.0188
True bifurcation (Medina 1.1.1, 1.0.1, and 0.1.1)	421 (46.5%)	834 (47.8%)	0.543	407 (46.7%)	405 (46.5%)	0.962	0.0046
IVUS usage	357 (39.4%)	706 (40.5%)	0.628	338 (38.8%)	333 (38.2%)	0.844	0.0117

Note: Values are expressed as mean ± standard deviation or n (%).
Abbreviations: CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, hsCRP = high-sensitivity C-reactive protein, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LDL = low-density lipoprotein cholesterol, LM = left main coronary artery, LVEF = left ventricular ejection fraction, IVUS = intravascular ultrasound, MI = myocardial infarction, NSTE-ACS = non-ST elevation acute coronary syndrome, PCI = percutaneous coronary intervention, PSM = propensity score matching, RCA = right coronary artery, SMD = standardized mean difference, STEMI = ST elevation myocardial infarction.

higher in the DM group. Examination of the individual components of TLF shows that the outcome differences between DM and non-DM groups were likely driven by TLR. Higher rates of TLF, representative of adverse outcomes at lesion level, have been observed in diabetic patients in various DES PCI studies [16]. DM generates hypercoagulable, pro-inflammatory and prothrombotic microenvironments, diffusely affecting vasculature inside the body, including coronary arteries [3, 4, 17]. The vascular wall, already under chronic inflammatory states from DM, undergoes further damage during PCI via mechanical stretch, endothelial denudation and subintimal hemorrhage [18]. Endothelial dysfunction in DM-damaged vessels then delays the healing processes that would safely implant the stents inside the coronary arteries, leading to higher rates of in-stent restenosis and the need for repeat revascularizations.

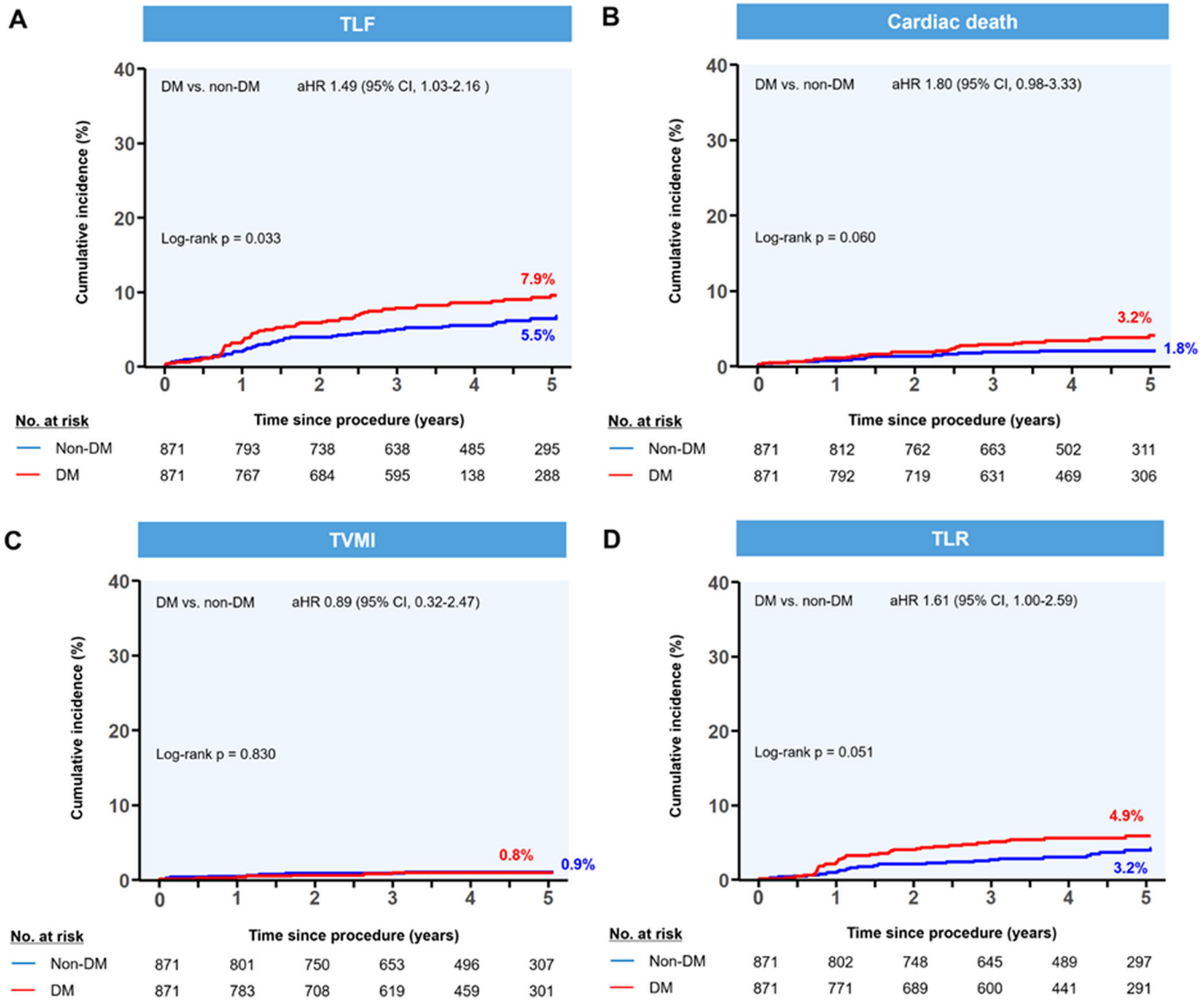

FIGURE 1 | Time-to-event curves according to the presence or absence of DM (A) TLF; (B) cardiac death; (C) TVMI; and (D) TLR. CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, TLR = target lesion revascularization, TVMI = target vessel myocardial infarction. [Color figure can be viewed at wileyonlinelibrary.com]

DM is also associated with plaque vulnerability. An analysis of IVUS imaging by Çakir et al. showed that vulnerable plaques such as thin-cap fibrous atheroma and attenuated plaques were more prevalent in DM patients compared with non-DM patients [19]. Positive correlations between attenuated plaques and HbA1c levels were also noted. In a Japanese registry study conducted in 2010, a 9-month follow-up after imaging-guided bifurcation PCI in DM and non-DM patients showed that late lumen loss in the proximal MV and SB were higher in DM patients [20].

Nonetheless, with newer stents and imaging devices, it appears that DM-induced disadvantages can be at least partially overcome [21]. Recently, TLF rates were reduced by imaging-guided PCI optimization in a randomized controlled study of imaging-guided versus angiography-guided PCI. Imaging-guided PCI yielded a 40% reduction in TLF risk in patients undergoing complex PCI, including PCI for bifurcation lesions [22]. In our study, the gap between DM and non-DM patients in TLF occurrence was diminished by IVUS usage; DM patients who underwent PCI using intracoronary imaging performed similar to non-DM patients undergoing imaging-guided PCI. Thus, the use of intracoronary imaging appears to benefit patients with diabetes. With this in consideration, it is not unreasonable that meticulous and well-planned PCI in DM patients delivers comparable results to those in non-DM patients.

Aside from DM, CKD, low LVEF and the application of a two-stent technique were independent predictors of MACE after PS matching. Both CKD and heart failure are well known risk factors of adverse outcomes after PCI, especially in high-risk and complex situations [23–26]. Studies on patients with severely reduced LVEF have even reported that the increased risks of PCI suggest inferiority of PCI over CABG in such patients [25]. Thus, bifurcation PCI in patients with CKD or LVEF < 50% should be performed with caution.

Generally, in bifurcation PCI, a provisional one-stent technique is favored over an upfront two-stent technique due to increased risks

TABLE 2 | Comparison of 5-year outcomes for DM versus non-DM groups.

	Pre-PSM				Post-PSM			
	DM ($N = 905$)	**Non-DM ($N = 1743$)**	**HR (95% CI)**	**Log-rank *p***	**DM ($N = 871$)**	**Non-DM ($N = 871$)**	**HR (95% CI)**	**Log-rank *p***
Primary outcome								
TLF*	77 (8.5%)	92 (5.3%)	1.69 (1.25; 2.29)	< 0.001	69 (7.9%)	48 (5.5%)	1.49 (1.03; 2.16)	0.033
Secondary outcomes								
MACE†	86 (9.5%)	104 (6.0%)	1.66 (1.25; 2.21)	< 0.001	76 (8.7%)	65 (7.5%)	1.20 (0.86; 1.67)	0.276
All-cause death	55 (6.1%)	59 (3.4%)	1.87 (1.30; 2.70)	< 0.001	48 (5.5%)	34 (3.9%)	1.46 (0.94; 2.27)	0.090
Cardiac death	31 (3.4%)	31 (1.8%)	2.00 (1.21; 3.29)	0.007	28 (3.2%)	16 (1.8%)	1.80 (0.98; 3.33)	0.060
MI	16 (1.8%)	24 (1.4%)	1.32 (0.70; 2.49)	0.384	14 (1.6%)	13 (1.5%)	1.10 (0.52; 2.34)	0.807
TVMI	8 (0.9%)	16 (0.9%)	1.00 (0.43; 2.33)	0.994	7 (0.8%)	8 (0.9%)	0.89 (0.32; 2.47)	0.830
TLR	48 (5.3%)	57 (3.3%)	1.71 (1.17; 2.5)	0.006	43 (4.9%)	28 (3.2%)	1.61 (1.00; 2.59)	0.051
TVR	71 (7.8%)	93 (5.3%)	1.55 (1.14; 2.12)	0.005	65 (7.5%)	47 (5.4%)	1.44 (0.99; 2.10)	0.056
ST	13 (0.7%)	12 (1.3%)	1.82 (0.83; 3.98)	0.136	11 (1.3%)	6 (0.7%)	1.86 (0.69; 5.03)	0.221
CVA	25 (2.8%)	27 (1.5%)	1.87 (1.08; 3.22)	0.025	23 (2.6%)	22 (2.5%)	1.08 (0.60; 1.93)	0.806

Note: Values are expressed as n (%) unless otherwise indicated. Cumulative incidence of events was presented as Kaplan-Meier estimates.
Abbreviations: CI = confidence interval, CVA = cerebrovascular accidents, DM = diabetes mellitus, HR = hazard ratio, MI = myocardial infarction, PSM = propensity score matching, ST = stent thrombosis, TLF = target lesion failure, TLR = target lesion revascularization, TVR = target vessel revascularization, TVMI = target vessel myocardial infarction.
*TLF was defined as a composite of cardiac death, TVMI and TLR.
†MACE was defined as a composite of all-cause death, MI and stroke.

TABLE 3 | Multivariable analysis for the occurrence of TLF[a] post PSM.

	Univariable			Multivariable		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age > 75	1.41	[0.92; 2.15]	0.116	1.17	[0.68; 2.03]	0.567
Male sex	1.26	[0.81; 1.95]	0.299	1.32	[0.76; 2.27]	0.321
DM	1.49	[1.03; 2.16]	0.032	1.57	[1.02; 2.43]	0.040
HTN	1.24	[0.84; 1.84]	0.278	1.22	[0.77; 1.94]	0.386
Current smoker	0.87	[0.57; 1.32]	0.510	0.78	[0.45; 1.33]	0.353
Dyslipidemia	0.97	[0.67; 1.41]	0.888	1.40	[0.90; 2.15]	0.131
CKD	3.84	[2.20; 6.72]	< 0.001	2.62	[1.27; 5.38]	0.008
Previous MI	1.25	[0.58; 2.68]	0.572			
Previous PCI	1.27	[0.81; 2.01]	0.300			
ACS presentation	0.90	[0.63; 1.30]	0.581	0.74	[0.47; 1.16]	0.183
LVEF < 50%	2.06	[1.35; 3.15]	< 0.001	1.92	[1.10; 3.35]	0.022
LDL > 100	0.61	[0.39; 0.96]	0.032	0.70	[0.44; 1.12]	0.139
hsCRP	1.00	[0.99; 1.02]	0.640			
LM disease	1.61	[1.09; 2.38]	0.016	1.27	[0.79; 2.05]	0.319
True bifurcation (Medina 1.1.1, 1.0.1, and 0.1.1)	0.96	[0.67; 1.39]	0.840			
IVUS usage	1.38	[0.96; 1.99]	0.078			
Two-stent technique	2.16	[1.46; 3.19]	< 0.001	2.18	[1.17; 4.05]	0.013
No. of stents	1.14	[0.97; 1.36]	0.121	0.99	[0.78; 1.26]	0.948
POT	0.93	[0.72; 1.19]	0.548			
FKB	1.81	[1.25; 2.61]	0.001	1.22	[0.69; 2.13]	0.496
Statin	0.63	[0.39; 1.01]	0.055	0.71	[0.39; 1.29]	0.264

Note: Values are expressed as *n* (%) unless otherwise indicated. Cumulative incidence of events was presented as Kaplan–Meier estimates.
Abbreviations: ACS = acute coronary syndrome, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, FKB = final kissing balloon, hsCRP = high sensitivity C-reactive protein, HR = hazard ratio, HTN = hypertension, LDL = low-density lipoprotein, LM = left main coronary artery, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PSM = propensity score matching, POT = proximal optimization technique.
[a]TLF was defined as a composite of cardiac death, TVMI and TLR.

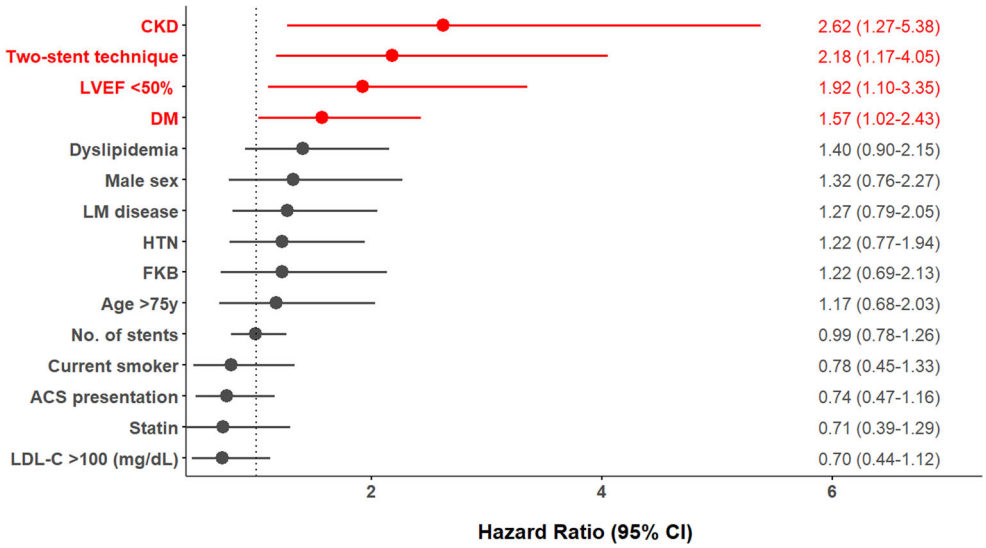

FIGURE 2 | Multivariable-adjusted model for MACE occurrence in bifurcation PCI. CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, FKB = final kissing balloon, HTN = hypertension, LDL = low-density lipoprotein cholesterol, LM = left main coronary artery, LVEF = left ventricular ejection fraction. [Color figure can be viewed at wileyonlinelibrary.com]

of procedural complication and adverse outcomes, supported by distinct bodies of evidence [27–30]. The results of our study suggest that an upfront two-stent strategy poses greater risk in patients with diabetes. Considering the inflammatory nature of DM that perhaps leads to a higher TLF prevalence, an increase in the number of stents or the complexity of procedure may cause harm. Nevertheless, the two-stented population often show differences in bifurcation anatomy and procedural methods. Some bifurcation lesions require definite preservation of the SBs, and the final decision should be left to the operator's discretion, based on the anatomy and other clinical characteristics of the patient.

Notably, although numerically higher in the DM group, the occurrence of MACE was not statistically different between the DM and non-DM groups after PS matching. Considering the "harder" outcome endpoints that constitute MACE (all-cause death, MI and CVA), the convergence may be attributed to the progress in medical care in recent years. The successes of sodium/glucose transporter 2 inhibitors and angiotensin receptor/neprilysin inhibitors have led to worldwide improvements in patients with diabetes and heart failure [31–33]. Stent platforms and designs have also evolved throughout the years, and the current generation of DES offers much more clinical and procedural stability than the bare-metal stents or the first-generation DES [34, 35]. Moreover, some stents have even demonstrated advantages over others in diabetic patients regarding cardiovascular outcomes [36].

This study has a few limitations. First, this was a registry cohort study without randomization. Thus, confounding factors such as selection bias could have affected the results. Second, the COBIS III registry is large and multicenter, but is based in a single country. Cautions should be taken, therefore, when extrapolating the results to patients with a non-Asian background. Third, while our analysis method of PS matching ensures that the sample closely resembles a randomized sample, DM is often accompanied by other potentially disabling or lifespan-shortening comorbidities. Decisions on revascularization strategies in real-life patients should be carefully planned for each individual, taking multiple factors into account.

In conclusion, this study demonstrated that even after matching for baseline characteristics, outcomes for patients with diabetes were worse than those without diabetes after PCI for coronary bifurcation lesions. However, careful planning and the use of intracoronary imaging devices may help improve outcomes for patients with DM.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.