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Original Article

Percutaneous coronary intervention versus coronary artery bypass grafting for unprotected left main true bifurcation lesions

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Abstract: Background: There are few studies comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for the treatment of bifurcation lesions of unprotected left main coronary artery (ULMCA). In the present study, we compared 1-year clinical outcomes of PCI with drug-eluting stent (DES) versus CABG in patients with ULMCA true bifurcation lesions. Methods: We evaluated a total of 276 consecutive patients with ULMCA true bifurcation lesions who underwent PCI with DES (n = 208) or CABG (n = 68). Propensity score (PS) adjustment and matching were applied to balance the baseline differences between groups. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE). Results: At 1 year, the incidence rate of MACCE was no significant difference between the PCI and CABG groups (12.5% vs. 19.1%, P = 0.163; PS-adjusted hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.37-1.63; P = 0.498); the rates of death (2.4% vs. 8.8%, P = 0.018) and the composite of death, myocardial infarction or stroke (7.7% vs. 17.6%, P = 0.019) were observed less frequently in the PCI group, which were no longer significantly different after PS adjustment (for death, PS-adjusted HR: 0.41, 95% CI: 0.11-1.61, P = 0.203; for the composite of death, myocardial infarction or stroke, PS-adjusted HR: 0.59, 95% CI: 0.25-1.37, P = 0.219). Conclusions: For the treatment of ULMCA true bifurcation lesions, PCI with DES was associated with similar 1-year clinical outcomes when compared with CABG.

Keywords: Percutaneous coronary intervention, coronary artery bypass grafting, unprotected left main, bifurcation lesions

Introduction

Significant unprotected left main coronary artery (ULMCA) disease, estimating of 5% patients undergoing coronary angiography [1], is associated with poor clinical outcomes and the optimal treatment of such patients remains uncertain [1, 2].

Coronary artery bypass grafting (CABG) has been considered the default approach for patients with ULMCA disease [3, 4]. However, with the accumulation of experience and improvements of technology and pharmacology, percutaneous coronary intervention (PCI), as an alternative to CABG, has been developed rapidly and broadly adopted for the treatment of ULMCA stenosis [1, 5]. Recently, several studies demonstrated that PCI and CABG were comparable in terms of the long-term incidence rates of death, myocardial infarction (MI), or stroke in selected situations [6-9]. Accordingly, current practice guidelines recommended PCI of ULMCA as Class IIa indication for the non-distal bifurcation lesions and as Class IIb indication for the distal bifurcation lesions [2, 3], indicating that the feasibility of PCI for complex ULMCA disease is still controversial.

ULMCA true bifurcation lesions (Medina classification types of 1.1.1, 1.0.1, 0.1.1) represent more complicated lesions subset and PCI for such lesions is technically challengeable for interventional cardiologists [10]. Despite that several recent studies have shown that PCI with modified stenting technique is associated with favorable clinical outcomes for treatment of true bifurcation lesions of ULMCA [10-12], there is no previous study to compare PCI (with DES) versus CABG in such disease subsets. Therefore, we conducted an observational cohort study to evaluate the clinical outcomes of PCI versus CABG in patients with ULMCA true bifurcation lesions.

Methods

Study population

This observational cohort study included 276 consecutive "all comers" patients with ULMCA true bifurcation lesions (≥50% diameter stenosis) diagnosed by angiography, and they were treated with either PCI with drug-eluting stents (DES) or CABG between November 2010 and January 2015. Declaration of Helsinki and approval of the protocol was obtained from the Medical Ethics Committee of Union Hospital, Fujian Medical University.

The revascularization strategy (PCI or CABG) was determined by an experienced heart team (interventional cardiologists and cardiac surgeons) based on clinical risk, angiographic characteristics and patient preference. All patients signed written informed consent.

Cardiac operative risk scores including European System for Cardiac Operative Risk Evaluation (EuroSCORE II), Society of Thoracic Surgeons (STS) score, and Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score were calculated for every patient.

Procedures

All interventional procedures were performed according to current practice guidelines. The stents were selected mainly from Resolute (Medtronic Cardiovascular, Santa Rosa, California), Xience V (Abbott Vascular, Santa Clara, California), Firebird-2 (Microport Co., Shanghai, China) and Excel (JW Medical System, Weihai, China). Bifurcation lesions were treated using one-stent technique or two-stent strategies such as T-stenting, mini-culotte, double kissing culotte (DK culotte), and double kissing crush (DK crush) [11-14]. The stenting strategy was at the discretion of operators according to the lesions characteristic and their experiences. Final kissing balloon dilation was performed in most cases and was mandatory in two-stent procedure. If necessary, additional stenting of other vessel lesions was performed to achieve complete revascularization. IABP was used in high-risk patients with severe heart failure. The use of IVUS and the choice of particular DES were at the discretion of the operators. All patients undergoing PCI were administered with a loading dose of aspirin (300 mg) plus clopidogrel (300 or 600 mg) or ticagrelor (180 mg) before or during intervention procedures. Periprocedural anticoagulation followed the standard treatment. During the procedure, patients received unfractionated heparin 100 IU/kg intravenously, which was corrected to maintain an activated clotting time > 300 seconds. Whether to use glycoprotein IIb/IIIa receptor inhibitor was left to the discretion of the operators. After discharge, all patients treated with PCI were prescribed a standard dual antiplatelet therapy regimen (aspirin 100 mg daily, and clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) for at least 12 months and continuing aspirin indefinitely.

CABG was performed using standard bypass techniques either on-pump or off-pump under general anesthesia. Arterial conduits and saphenous vein grafts were used in most cases to gain complete revascularization. When possible, left internal mammary artery (LIMA) was harvested for the left anterior descending coronary artery revascularization. If patients had been taking aspirin and clopidogrel, CABG would be delayed for 5 days after the cessation of clopidogrel. After CABG, aspirin 100 mg per day was continued indefinitely.

Other postprocedure medication treatments such as statins, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and beta blockers were prescribed to patients undergoing PCI or CABG according to current clinical practice.

Follow-up

Clinical follow-up was scheduled at 1, 6, and 12 months after revascularization and then annually thereafter. Routine angiographic follow-up was recommended at 12 months after PCI. Angiography was performed beforehand if symptoms of angina recurred. For patients who underwent CABG, routine follow-up angiography was not recommended, and was suggested

Table 1. Baseline clinical characteristics

Variables	Total Population			Propensity-Matched Population		
	PCI (n = 208)	CABG (n = 68)	*P* Value	PCI (n = 58)	CABG (n = 58)	*P* Value
Age, years	65.0 ± 9.4	64.5 ± 8.7	0.660	63.9 ± 10.3	64.5 ± 8.5	0.747
Male	180 (86.5)	56 (82.4)	0.395	48 (82.8)	47 (81.0)	0.809
Hypertension	128 (61.5)	48 (70.6)	0.178	40 (69.0)	41 (70.7)	0.840
Systolic BP, mmHg	130.9 ± 18.7	130.0 ± 16.9	0.724	128.1 ± 19.8	129.9 ± 17.5	0.589
Diastolic BP, mmHg	78.4 ± 10.8	77.7 ± 10.9	0.636	77.7 ± 10.3	77.3 ± 11.6	0.832
Diabetes	62 (29.8)	31 (45.6)	0.017	21 (36.2)	22 (37.9)	0.848
Insulin-dependent	11 (5.3)	5 (7.4)	0.527	4 (6.9)	4 (6.9)	1.000
Fasting glucose, mmol/L	5.76 ± 1.76	6.60 ± 3.33	0.008	6.35 ± 2.56	6.07 ± 1.93	0.509
Hyperlipidaemia	92 (44.2)	32 (47.1)	0.684	33 (55.9)	26 (44.8)	0.194
TC, mmol/L	4.32 ± 1.21	4.47 ± 1.14	0.370	4.64 ± 1.37	4.47 ± 1.04	0.445
LDL-C, mmol/L	2.80 ± 1.10	2.85 ± 1.01	0.721	3.05 ± 1.28	2.92 ± 0.96	0.529
Triglyceride, mmol/L	1.44 ± 0.94	1.61 ± 1.74	0.284	1.63 ± 1.33	1.27 ± 0.49	0.059
Smoking	107 (49.6)	30 (44.1)	0.294	29 (50.0)	27 (46.6)	0.710
Current smoking	72 (34.6)	21 (30.9)	0.572	20 (34.5)	19 (32.8)	0.844
COPD	21 (10.1)	4 (5.9)	0.293	3 (5.2)	4 (6.9)	1.000
Stroke	11 (5.3)	6 (8.8)	0.381	4 (6.9)	4 (6.9)	1.000
Peripheral vascular disease	12 (5.8)	6 (8.8)	0.399	5 (8.6)	4 (6.9)	1.000
Malignancy	9 (4.3)	1 (1.5)	0.459	1 (1.7)	1 (1.7)	1.000
Previous MI	44 (21.2)	15 (22.1)	0.874	11 (19.0)	12 (20.7)	0.816
Previous PCI	43 (20.7)	10 (14.7)	0.278	10 (17.2)	8 (13.8)	0.608
Serum creatinine, μmol/L	84.2 ± 22.5	81.5 ± 23.5	0.402	81.9 ± 30.6	80.5 ± 22.4	0.785
LVEF, %	59.1 ± 12.3	58.7 ± 12.2	0.822	58.8 ± 13.1	58.3 ± 12.2	0.826
Clinical indication			0.144			0.181
Stable angina pectoris	25 (12.0)	5 (7.4)		7 (12.1)	3 (5.2)	
Unstable angina	142 (68.3)	51 (75.0)		36 (62.1)	46 (79.3)	
Non-STEMI	24 (11.5)	3 (4.4)		6 (10.3)	2 (3.4)	
STEMI	17 (8.2)	9 (13.2)		9 (15.5)	7 (12.1)	

Values are mean ± SD or n (%). PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; BP = blood pressure; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

only for ischemic clinical presentation during follow-up. Subjects who had not adhered to the recommended follow-up processes were interviewed by telephone.

Study endpoints and definitions

The primary endpoint of this study was a patient-oriented composite of major adverse cardiac and cerebrovascular event (MACCE) at 1-year follow-up, which included all-cause death, myocardial infarction (MI), stroke or target vessel revascularization (TVR). In the analysis of cumulative endpoints, events were counted only once, whichever occurred first.

The secondary endpoints were a composite safety endpoint of all-cause death/MI/stroke, individual components of MACCE, and stent thrombosis (ST) or graft occlusion (GO).

Death was defined as postprocedure death from any cause and classified as from either cardiac or noncardiac causes, according to the Academic Research Consortium (ARC) definition [15]. Death was considered as cardiac origin unless a noncardiac origin had definitely been proved. Cardiac death was defined as any death due to a cardiac cause (e.g., MI, low-output heart failure, fatal arrhythmias), procedure-related death, or death of unknown cause.

MI was defined according to the third universal definition of myocardial infarction [16]. Evidences for MI mainly included elevated cardiac troponin (cTn) with at least one value above

Table 2. Lesion characteristics and procedural risk scores

Variables	Total Population			Propensity-Matched Population		
	PCI (n = 208)	CABG (n = 68)	*P* Value	PC (n = 58)	CABG (n = 58)	*P* Value
LMCA lesion location						
Bifurcation + ostial	23 (11.1)	5 (7.4)	0.380	4 (6.9)	5 (8.6)	1.000
Bifurcation + midshaft	38 (18.3)	13 (19.1)	0.876	9 (15.5)	12 (20.7)	0.469
Bifurcation + whole trunk	20 (9.6)	5 (7.4)	0.573	4 (6.9)	5 (8.6)	1.000
LMCA distal bifurcation type			0.210			1.000
Medina 1.1.1	137 (65.9)	51 (75.0)		12 (20.7)	11 (19.0)	
Medina 1.0.1	12 (5.8)	5 (7.4)		4 (6.9)	5 (8.6)	
Medina 0.1.1	59 (28.4)	12 (17.6)		42 (72.4)	42 (72.4)	
LMCA restenosis	7 (3.4)	2 (2.9)	1.000	2 (3.4)	1 (1.7)	1.000
RCA disease	146 (70.2)	60 (88.2)	0.003	46 (79.3)	50 (86.2)	0.326
Total occlusion	56 (26.9)	31 (45.6)	0.004	23 (39.7)	23 (39.7)	1.000
Total occlusion in RCA	29 (13.9)	16 (23.5)	0.063	12 (20.7)	11 (19.0)	0.816
SYNTAX score, points	28.4 ± 7.8	31.9 ± 7.7	0.002	31.2 ± 7.0	31.0 ± 7.6	0.889
Euro SCORE II, %	3.26 ± 3.61	3.61 ± 3.53	0.482	4.14 ± 5.19	3.56 ± 3.24	0.472
STS score, %	2.99 ± 3.33	3.56 ± 3.60	0.231	3.92 ± 4.82	3.46 ± 3.24	0.548

Values are n (%) or mean ± SD. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; LMCA = left main coronary artery; RCA = right coronary artery.

the 99th percentile upper reference limit (URL), symptoms of myocardial ischemia, electrocardiographic changes and angiographic characteristics. Within 48 h following the procedure, cTn values above 5 times the 99th percentile URL after PCI or 10 times after CABG were used to define periprocedural PCI or CABG related MI in patients with normal baseline cTn levels (≤99th percentile URL). If the baseline values were elevated and were stable or falling, a rise of cTn values > 20% was also considered evidence of periprocedural PCI related MI. Q-wave MI was defined as MI together with a new pathologic Q-wave in no less than 2 contiguous leads after index treatment.

Cerebrovascular events included both ischemic and hemorrhagic stroke confirmed by neurologists on the basis of clinical symptoms such as neurological deficits and the imaging study findings.

TVR was defined as any surgical or percutaneous repeat revascularization of any segment of the stented vessel (target lesion, upstream or downstream branches) within 1-year, including the left main, left anterior descending and left circumflex coronary arteries. A planned staged PCI was not considered as a TVR.

The occurrence of definite, probable or possible stent thrombosis (ST) was defined according to the ARC definition (for PCI), and graft occlusion was defined according to ARC-like definition (for CABG) [17].

Statistical methods

Continuous variables were presented as mean ± SD, and categorical variables were presented as number (%). Comparisons between the PCI and CABG groups in baseline characteristics were performed by t-test or Wilcoxon rank-sum test for continuous data, and chi-square test or Fisher's exact test for categorical data, as appropriate. Cumulative event curves of the PCI and CABG groups were constructed by Kaplan-Meier method and were compared using log-rank test. Hazard ratios (HR) together with 95% confidence intervals (CI) were calculated using Cox proportional hazard models.

Propensity score (PS) adjustment and matching were applied to compensate the treatment selection bias between the PCI and CABG groups in this observational study. We used a multivariate logistic regression model to calculate the PS of every patient. A full nonparsimonious model was developed. The covariates were the baseline characteristics in **Tables 1** and **2**. The discrimination of the PS model was accessed with c-statistic, and its calibration was assessed with Hosmer-Lemeshow statistic. We used Cox proportional hazard models,

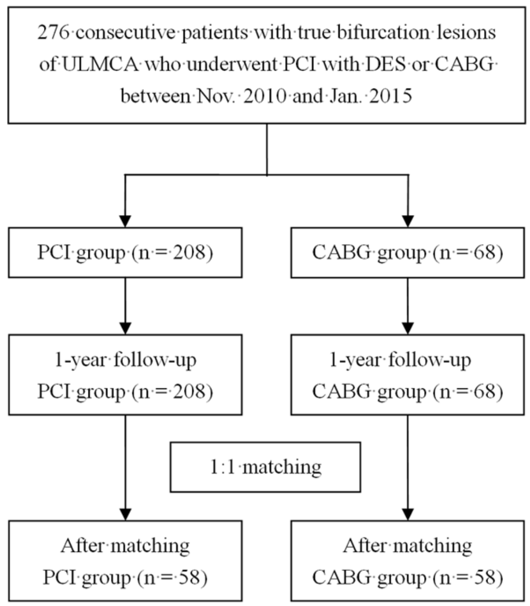

Figure 1. Study Flowchart. ULMCA = unprotected left main coronary artery; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

with PS as a covariate, to estimate the PS-adjusted HR and 95% CI. Furthermore, we performed a 1:1 PS matching with the nearest neighbor method within a caliper width equal to 0.2 times the standard deviation of the logit of the PS [18].

In the pre-specified subgroups, the interactions were calculated using Cox regression models to evaluate the heterogeneity of treatment effect among subgroups, and the treatment outcomes with respect to MACCE between the PCI and CABG groups were compared using Cox regression models with PS adjustment.

A *P* value < 0.05 was considered significant, and all tests were two-tailed. All the statistical analysis were performed with SPSS software (version 22.0, SPSS, IBM Corporation, Armonk, New York).

Results

Baseline characteristics

Overall population: Between November 2010 and January 2015, a total of 276 consecutive patients with ULMCA true bifurcation lesions received PCI with DES (n = 208) or CABG (n = 68), all these patients were completely followed up for at least 1 year (**Figure 1**). Baseline clinical characteristics, angiographic characteristics and cardiac operative risk scores are shown in **Tables 1** and **2**. Patients in the PCI group had a mean age of 65.0 ± 9.4 years with 180 (86.5%) men, and patients in the CABG group had a mean age of 64.5 ± 8.7 years with 56 (82.4%) men. Compared with patients in the CABG group, patients treated with PCI less frequently suffered diabetes mellitus (29.8% vs. 45.6%, P = 0.017), total occlusion (26.9% vs. 45.6%, P = 0.004) and RCA disease (70.2% vs. 88.2%, P = 0.003), and they had lower fasting blood glucose (FBG) levels (5.76 ± 1.76 mmol/L vs. 6.60 ± 3.33 mmol/L, P = 0.008), as well as SYNTAX scores (28.4 ± 7.8 vs. 31.9 ± 7.7, P = 0.002). There were no significant differences between two groups in other clinical characteristics, angiographic characteristics and cardiac operative risk scores.

Propensity-matched population

The c-statistic of this propensity score model was 0.770, and Hosmer-Lemeshow goodness of fit test *P* value was 0.924, which shows that this propensity score model has good discrimination and calibration. After PS matching, 58 patients treated with PCI were matched with 58 patients treated with CABG (**Tables 1** and **2**). Baseline characteristics between the PCI and CABG groups were all similar in the propensity-matched population.

Procedural characteristics

In the PCI group, 96 (46.2%) patients received one-stent technique, and 112 (53.8%) patients received two-stent techniques (mainly including T, mini-culotte, DK culotte and DK crush stenting); IVUS was used in 63 (30.3%) patients, and IABP was used in 5 (2.4%) patients with severe heart failure; the mean numbers of implanted stents in main vessels and side branch vessels of LMCA were 1.47 ± 0.66 and 0.62 ± 0.54, respectively.

Among CABG patients, 42 (61.8%) patients underwent off-pump surgery; 67 (98.5%) patients received a graft to the LAD with 58 (85.3%) cases of LIMA-to-LAD grafting, and 40 (58.8%) patients received a graft to the LCX; IABP was used in 2 (2.4%) patients who suffered severe heart failure.

Table 3. Procedural characteristics

Procedural variables	Total Population	Propensity-Matched Population
PCI-related, n	208	58
Radial access	144 (69.2)	36 (62.1)
Bifurcation stenting		
One-stent technique	96 (46.2)	25 (43.1)
Two-stent techniques	112 (53.8)	33 (56.9)
T-stenting	35 (16.8)	13 (22.4)
Culotte	51 (24.5)	13 (22.4)
Double kissing Culotte	19 (9.1)	6 (10.3)
Double kissing Crush	16 (7.7)	4 (6.9)
Other	10 (4.8)	3 (5.2)
Main vessel stent		
n	1.47 ± 0.66	1.47 ± 0.66
Maximum diameter, mm	3.61 ± 0.42	3.59 ± 0.44
Total length, mm	37.4 ± 19.6	36.0 ± 18.7
Side branch stent		
n	0.62 ± 0.54	0.67 ± 0.51
Maximum diameter, mm	3.12 ± 0.44	3.11 ± 0.48
Total length, mm	23.0 ± 10.7	21.9 ± 9.1
Final kissing balloon dilatation	139 (66.8)	40 (69.0)
Stenting for RCA	33 (15.9)	10 (17.2)
IABP support	5 (2.4)	4 (6.9)
IVUS assessment	63 (30.3)	19 (32.8)
CABG-related, n	68	58
Off-pump surgery	42 (61.8)	35 (60.3)
Graft per patient, n	2.54 ± 0.70	2.59 ± 0.70
Graft for LAD	67 (98.5)	58 (100)
IMA-to-LAD	58 (85.3)	50 (86.2)
Graft for LCX	40 (58.8)	32 (55.2)
Graft for RCA	41 (60.3)	37 (63.8)
IABP support	2 (2.9)	2 (3.4)

Values are n (%) or mean ± SD. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; RCA = right coronary artery; IABP = intra-aortic ballon pump; IVUS = intravascular ultrasound; LAD = left anterior descending; IMA = internal mammary artery; LCX = left circumflex.

Detailed procedural characteristics for overall population together with propensity-matched population are summarized in **Table 3**.

Clinical outcomes

Overall population: During 1-year follow-up, 14 (5.1%) patients suffered MI, 5 (1.8%) patients suffered stroke, 16 (5.8%) patients received TVR, 11 (4.0%) patients died, and cumulative MACCE occurred in a total of 39 (14.1%) patients. The cumulative clinical outcomes of the PCI and CABG groups are shown in **Table 4** and **Figure 2**.

At 30 days, the cumulative incidence of MACCE was 6.2% in the PCI group versus 10.3% in the CABG group. There were no significant differences in the rates of MACCE, the composite of death/MI/stroke, individual MI, TVR and ST/GO between the PCI and CABG groups. Death was less likely to occur after PCI than after CABG (1.4% vs. 5.9%, P = 0.045). Similarly, the occurrence of stroke was significantly lower in the PCI group than in the CABG group (0.5% vs. 4.4%, P = 0.019). However, there were no statistically significant differences between the two groups in the PS-adjusted risks of death (PS-adjusted HR: 0.39, 95% CI: 0.07-2.17; P = 0.282) and stroke (PS-adjusted HR: 0.17, 95% CI: 0.01-2.01; P = 0.166).

At 1 year, the cumulative MACCE occurred in 12.5% patients undergoing PCI compared with 19.1% patients undergoing CABG (log-rank P = 0.163; PS-adjusted HR: 0.77, 95% CI: 0.37-1.63; P = 0.498). Though the incidence of the composite of death/MI/stroke was significantly lower in the PCI group than in the CABG group (7.7% vs. 17.6%, P = 0.019), there was no significant difference in the PS-adjusted risk of death/MI/stroke between the PCI and CABG groups (PS-adjusted HR: 0.59, 95% CI: 0.25-1.37; P = 0.219). The rates of MI (4.8% vs. 5.9%, P = 0.714), stroke (1.0% vs. 4.4%, P = 0.060), TVR (6.7% vs. 2.9%, P = 0.282) and ST/GO (4.3% vs. 5.9%, P = 0.574) were all comparable between the PCI and CABG groups. Though death occurred less frequently in the PCI group than in the CABG group (2.4% vs. 8.8%, P = 0.018), the PS-adjusted risk of death also had no statistically significant difference

Table 4. Clinical outcomes at follow-up (total population)

Outcome	PCI (n = 208)	CABG (n = 68)	Log-rank *P* Value	Unadjusted		PS Adjusted	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
30 days							
Composite MACCE	13 (6.2)	7 (10.3)	0.278	0.61 (0.24-1.52)	0.284	0.94 (0.33-2.66)	0.904
Death/MI/Stroke	12 (5.8)	7 (10.3)	0.212	0.56 (0.22-1.42)	0.220	0.82 (0.28-2.35)	0.709
All-cause death	3 (1.4)	4 (5.9)	0.045	0.24 (0.06-1.09)	0.065	0.39 (0.07-2.17)	0.282
Cardiac death	3 (1.4)	3 (4.4)	0.149	0.33 (0.07-1.62)	0.171	0.56 (0.09-3.57)	0.543
MI	8 (3.8)	1 (1.5)	0.340	2.64 (0.33-21.09)	0.360	2.98 (0.33-27.29)	0.334
STEMI	3 (1.4)	1 (1.5)	0.984	0.98 (0.10-9.39)	0.984	1.25 (0.10-15.65)	0.862
Sroke	1 (0.5)	3 (4.4)	0.019	0.11 (0.01-1.04)	0.054	0.17 (0.01-2.01)	0.166
TVR	4 (1.9)	0 (0.0)	0.254	-	0.487	-	0.974
ST/GO	6 (2.9)	1 (1.5)	0.521	1.97 (0.24-16.36)	0.530	2.14 (0.22-21.03)	0.514
1 year							
Composite MACCE	26 (12.5)	13 (19.1)	0.163	0.63 (0.32-1.22)	0.168	0.77 (0.37-1.63)	0.498
Death/MI/Stroke	16 (7.7)	12 (17.6)	0.019	0.42 (0.20-0.89)	0.024	0.59 (0.25-1.37)	0.219
All-cause death	5 (2.4)	6 (8.8)	0.018	0.27 (0.08-0.87)	0.028	0.41 (0.11-1.61)	0.203
Cardiac death	4 (1.9)	4 (5.9)	0.090	0.32 (0.08-1.29)	0.108	0.63 (0.13-3.01)	0.565
MI	10 (4.8)	4 (5.9)	0.714	0.81 (0.25-2.57)	0.715	0.88 (0.24-3.20)	0.844
STEMI	3 (1.4)	1 (1.5)	0.984	0.98 (0.10-9.39)	0.984	1.25 (0.10-15.65)	0.862
Sroke	2 (1.0)	3 (4.4)	0.060	0.21 (0.04-1.26)	0.088	0.27 (0.04-2.01)	0.201
TVR	14 (6.7)	2 (2.9)	0.282	2.21 (0.50-9.72)	0.295	2.47 (0.51-12.05)	0.264
ST/GO	9 (4.3)	4 (5.9)	0.574	0.72 (0.22-2.32)	0.576	0.79 (0.21-2.95)	0.727

Values are n (%) unless otherwise indicated. Outcome rates are Kaplan-Meier estimates with *P* values from log-rank test, Unadjusted and propensity score (PS) adjusted hazard ratio (HR) with their respective *P* values are derived from Cox regression analysis. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization; ST = stent thrombosis; GO = graft occlusion.

between the two groups (PS-adjusted HR: 0.41, 95% CI: 0.11-1.61; P = 0.203).

Propensity-matched population

After PS matching, the incidence of MACCE was similar between the PCI and CABG groups at 30 days (8.6% vs. 6.9%, P = 0.711) or at 1 year (12.1% vs. 13.8%, P = 0.820). PS-adjusted HR at 1 year was 0.90 (95% CI: 0.33-2.48; P = 0.498). All endpoints were all comparable both at 30 days and at 1 year between the two groups (**Table 5** and **Figure 3**).

Subgroup analysis

The results of subgroup analysis are presented in **Table 6**. There were no significant interactions between the revascularization strategy (PCI and CABG) and MACCE among all the subgroups. Compared with the CABG group, the cumulative event rate of MACCE was significantly lower in the PCI group in the subgroup of aged patients (10.3% vs. 27.0%, P = 0.010), and a similar result was found in the subgroup of patients with diabetes mellitus (11.3% vs. 29.0%, P = 0.032). However, PS-adjusted risks of MACCE were both no statistically significant differences between the PCI and CABG groups in the above two subgroups (PS-adjusted HR: 0.46, 95% CI: 0.18-1.19; P = 0.110; PS-adjusted HR: 0.45, 95% CI: 0.15-1.37; P = 0.157, respectively). Additionally, in either unadjusted or PS-adjusted analysis, the rates of MACCE were all comparable between the PCI and CABG groups in other subgroups.

Discussion

In the present observational cohort study, we firstly compared the 1-year clinical outcomes after PCI with DES or CABG in patients with ULMCA true bifurcation lesions. The main finding of this study is that PCI (with DES) was associated with a similar incidence of MACCE when compared with CABG. In addition, we

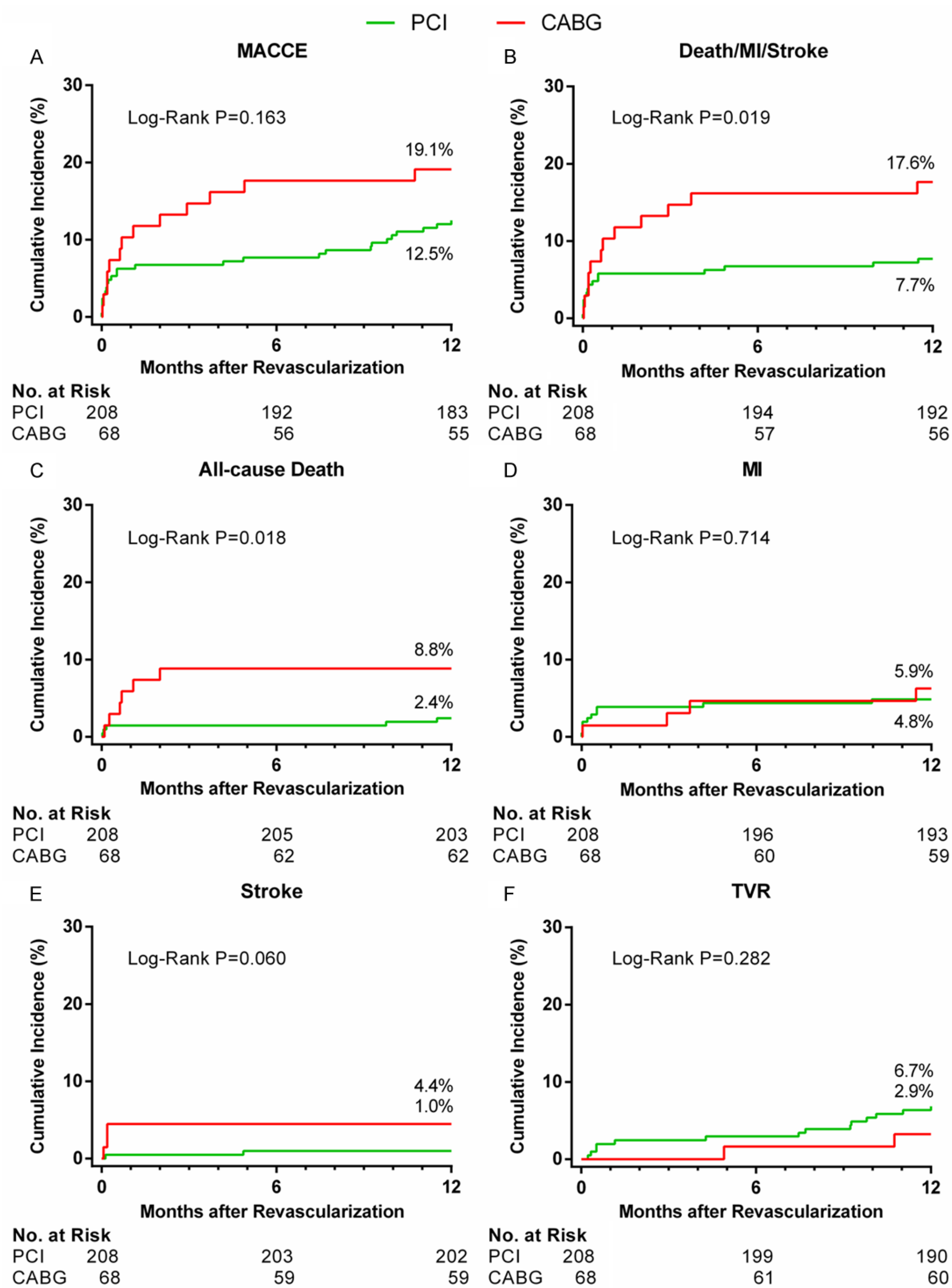

Figure 2. Kaplan-Meier curves for adverse events at 1-year follow-up in the total population. Kaplan-Meier curves for (A) major adverse cardiac and cerebrovascular event (MACCE), (B) all-cause death/myocardial infarction (MI)/stroke, (C) all-cause death, (D) MI, (E) stroke, (F) target vessel revascularization (TVR) in the total population. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

Table 5. Clinical outcomes at follow-up (propensity-matched population)

Outcome	PCI (n = 58)	CABG (n = 58)	Log-rank *P* Value	Unadjusted		PS Adjusted	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
30 days							
Composite MACCE	5 (8.6)	4 (6.9)	0.711	1.28 (0.34-4.78)	0.712	1.30 (0.35-4.83)	0.699
Death/MI/Stroke	4 (6.9)	4 (6.9)	0.980	1.02 (0.26-4.07)	0.980	1.03 (0.26-4.11)	0.972
All-cause death	3 (5.2)	3 (5.2)	0.980	1.02 (0.21-5.06)	0.980	1.04 (0.21-5.14)	0.965
Cardiac death	3 (4.4)	2 (3.4)	0.638	1.53 (0.26-9.17)	0.640	1.55 (0.26-9.30)	0.631
MI	1 (1.7)	1 (1.7)	0.990	1.02 (0.06-16.28)	0.990	0.98 (0.06-15.75)	0.991
STEMI	0 (0.0)	1 (1.7)	0.317	-	0.610	-	0.978
Sroke	0 (0.0)	1 (1.7)	0.326	-	0.614	-	0.978
TVR	1 (1.7)	0 (0.0)	0.309	-	0.607	-	0.978
ST/GO	1 (1.7)	1 (1.7)	0.990	1.02 (0.06-16.28)	0.990	0.98 (0.06-15.75)	0.991
1 year							
Composite MACCE	7 (12.1)	8 (13.8)	0.820	0.89 (0.32-2.45)	0.820	0.90 (0.33-2.48)	0.836
Death/MI/Stroke	4 (6.9)	7 (12.1)	0.372	0.58 (0.17-1.97)	0.379	0.58 (0.17-1.99)	0.387
All-cause death	3 (5.2)	5 (8.6)	0.491	0.61 (0.15-2.54)	0.496	0.63 (0.15-2.64)	0.526
Cardiac death	3 (5.2)	3 (5.2)	0.986	1.02 (0.21-5.03)	0.986	1.05 (0.21-5.20)	0.955
MI	1 (1.7)	2 (3.4)	0.567	0.50 (0.05-5.54)	0.575	0.48 (0.04-5.32)	0.551
STEMI	0 (0.0)	1 (1.7)	0.317	-	0.610	-	0.978
Sroke	0 (0.0)	1 (1.7)	0.326	-	0.614	-	0.978
TVR	3 (5.2)	1 (1.7)	0.311	3.04 (0.32-29.24)	0.335	3.07 (0.32-29.56)	0.331
ST/GO	1 (1.7)	2 (3.4)	0.567	0.50 (0.05-5.55)	0.575	0.48 (0.04-5.32)	0.551

Values are n (%) unless otherwise indicated. Outcome rates are Kaplan-Meier estimates with *P* values from log-rank test, Unadjusted and propensity score (PS) adjusted hazard ratio (HR) with their respective *P* values are derived from Cox regression analysis. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization; ST = stent thrombosis; GO = graft occlusion.

found that the rates of a composite safety endpoint of all-cause death/MI/stroke, individual components of MACCE, and ST/GO were all comparable between the PCI and CABG groups. Therefore, PCI appears to be a feasible alternative to CABG for the treatment of ULMCA true bifurcation lesions.

Many observational studies demonstrated that PCI was not inferior to CABG for the treatment of left main disease [19-22]. The 1-year to 5-year substudy for left main in the randomized SYNTAX trial also showed similar outcomes with respect to MACCE as well as the composite safety endpoint of all-cause death/MI/stroke between the PCI and CABG groups [6, 7], and these results above were further supported by the 1-year to 5-year outcomes of the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial [8, 9]. Though left main bifurcation lesions, especially true bifurcation lesions, were complex and associated with worse clinical outcomes compared with ostial/mid-shaft lesions [23-27], an observational study indicated that PCI using DES provided similar long-term clinical outcomes (composite of death, Q-wave myocardial infarction, or stroke) except for TVR compared with CABG in patients with left main bifurcation lesions (Medina 1.1.1, 1.1.0 and 1.0.1) [28]. In our study, we found that PCI with DES was associated with similar rates of 1-year MACCE and the composite of all-cause death/MI/stroke compared with CABG for the treatment of ULMCA true bifurcation lesions, which were consistent with the results of the above studies. Interestingly, the composite of death/MI/stroke was observed significantly less frequently after PCI than after CABG in this study, which was consistent with a recent observational study regarding ULMCA disease from China [29], but not consistent with the usual result. We speculated that this finding might be mainly attributed to the high SYNTAX scores in patients

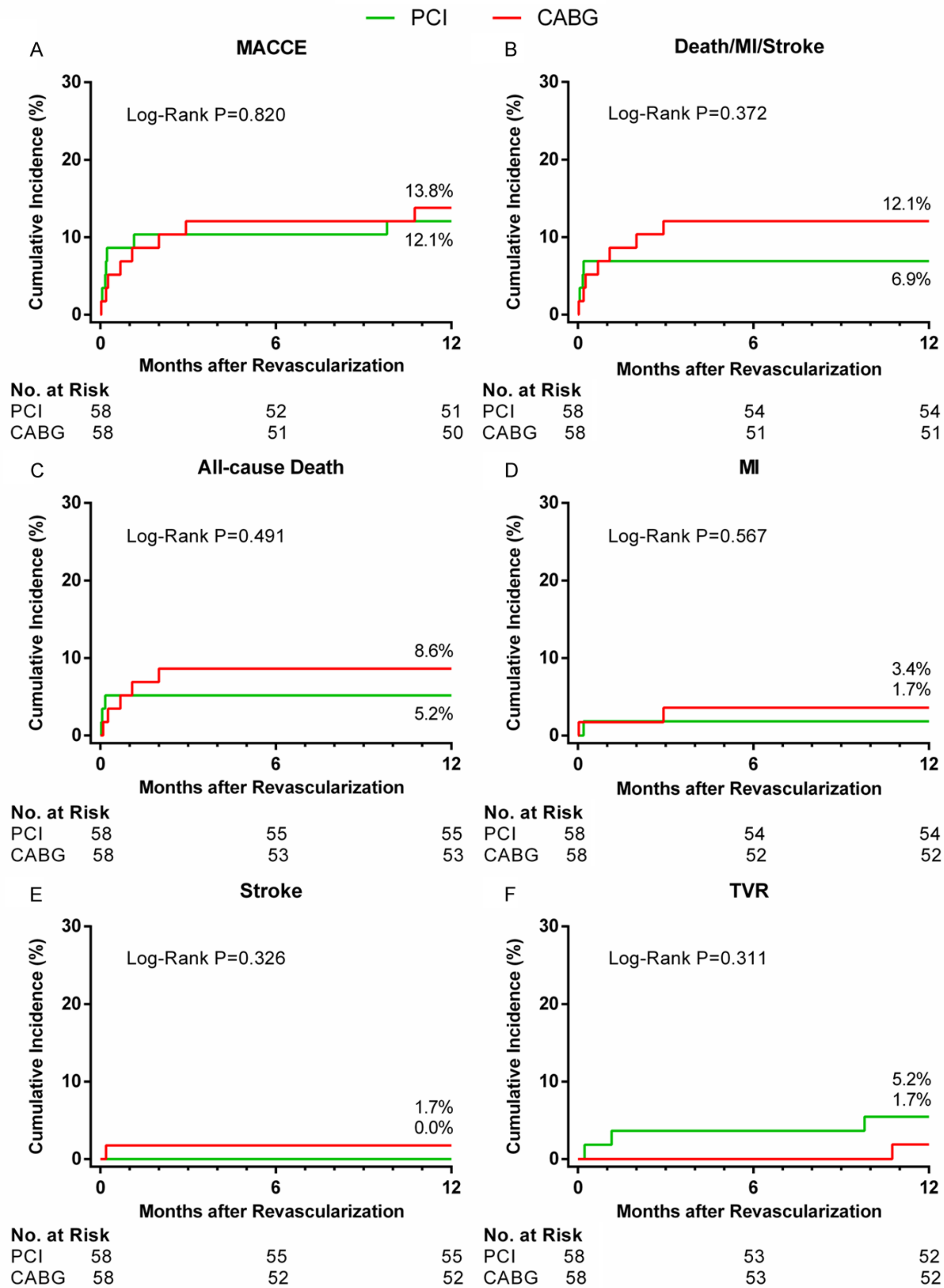

Figure 3. Kaplan-Meier curves for adverse events at 1-year follow-up in propensity-matched population. Kaplan-Meier curves for (A) major adverse cardiac and cerebrovascular event (MACCE), (B) all-cause death/myocardial infarction (MI)/stroke, (C) all-cause death, (D) MI, (E) stroke, (F) target vessel revascularization (TVR) in propensity-matched population. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

Table 6. Hazard ratio for 1-year MACCE in pre-specified subgroups in total population

Subgroup	No./Total No. (%)		Log-rank *P* Value	Unadjusted		PS Adjusted		Interaction *P* Value
	PCI	CABG		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
Overall	26/208 (12.5)	13/68 (19.1)	0.163	0.63 (0.32-1.22)	0.168	0.77 (0.37-1.63)	0.498	
Gender								0.477
Male	22/180 (12.2)	12/56 (21.4)	0.075	0.53 (0.26-1.08)	0.080	0.73 (0.32-1.63)	0.437	
Female	4/24 (14.3)	1/12 (8.3)	0.593	1.80 (0.20-16.14)	0.598	1.55 (0.16-14.93)	0.706	
Age								0.454
<65 years	14/91 (15.4)	3/31 (9.7)	0.450	1.61 (0.46-5.60)	0.455	1.77 (0.47-6.64)	0.395	
≥65 years	12/117 (10.3)	10/37 (27.0)	0.010	0.35 (0.15-0.81)	0.014	0.46 (0.18-1.19)	0.110	
Diabetes								0.789
Yes	7/62 (11.3)	9/31 (29.0)	0.032	0.36 (0.13-0.96)	0.041	0.45 (0.15-1.37)	0.157	
No	19/146 (13.0)	4/37 (10.8)	0.737	1.20 (0.41-3.54)	0.738	1.29 (0.41-4.05)	0.665	
SYNTAX score								0.438
0-32	17/145 (11.7)	5/34 (14.7)	0.623	0.78 (0.29-2.11)	0.624	0.71 (0.24-2.04)	0.519	
≥33	9/63 (14.3)	8/34 (23.5)	0.262	0.58 (0.23-1.51)	0.268	0.99 (0.33-2.96)	0.985	
LVEF								0.601
<50%	6/45 (13.3)	5/17 (29.4)	0.167	0.44 (0.14-1.45)	0.179	0.64 (0.16-2.53)	0.527	
≥50%	20/163 (12.3)	8/51 (15.7)	0.498	0.75 (0.33-1.71)	0.500	0.87 (0.35-2.15)	0.760	
AMI								0.845
Yes	5/41 (12.2)	4/12 (33.3)	0.090	0.34 (0.09-1.26)	0.107	0.48 (0.10-2.25)	0.352	
No	21/167 (12.6)	9/56 (16.1)	0.495	0.76 (0.35-1.67)	0.497	0.90 (0.38-2.13)	0.804	

Outcome rates are Kaplan-Meier estimates with *P* values from log-rank test. Unadjusted and propensity score (PS) adjustedhazard ratios (HR) with their respective *P* values, and interaction *P* values are derived from Cox regression analysis. Aninteraction *P* value represents the likelihood of interaction between the variable and the relative treatment effect. MACCE =major adverse cardiac and cerebrovascular events; PCI = percutaneous coronary intervention; CABG = coronary artery bypassgrafting; LVEF = left ventricular ejection fraction; AMI = acute myocardial infarction.

received CABG, the difference among ethnicities, and the different experiences of cardiologists among countries and regions.

PCI is almost always associated with an increased incidence of TVR compared with CABG in patients with left main or left main bifurcation lesions, and TVR is usually the main cause of MACCE after PCI [5-9]. In the current study, cumulative incidence of TVR at 1 year was numerically higher in the PCI group when compared to CABG group, but this difference did not reach a statistical significance. This finding was in agreement with the result of 1-year TVR in the PRECOMBAT study. Limited sample size should be an important reason for this result, but the low incidence of TVR may be the main cause. The 1-year rate of TVR after PCI in our study (6.7%) was similar to that in the PRECOMBAT study (6.1%), but was obviously lower than that in the SYNTAX substudy (12.0%).

Notably, our study was specifically aimed at true bifurcation lesions of ULMCA, which were more complex and usually associated with worse outcomes including an increased rate of TVR. However, the incidence of TVR after PCI in our study was relatively lower. It may be attributed to the following reasons. Firstly, stenting strategies and techniques for ULMCA disease have been well recognized and improved. Recent studies have demonstrated that conventional crush stenting was associated with worse outcomes compared with culotte stenting for the treatment of left main bifurcation lesions [30], and DK crush stenting was superior to conventional crush, culotte and provisional stenting for the treatment of true bifurcation lesions of ULMCA [11, 12, 31-33]. In addition, we have found that modified mini-culotte or DK culotte stenting might result in beneficial clinical outcomes in patients with coronary bifurcation lesions [13, 14]. Therefore, inappropriate stenting techniques such as conventional crush stenting were avoided as far as possible and improved stenting techniques such as modified mini-culotte, DK culotte and DK crush stenting were applied in the present study. Secondly, new zotarolimus-eluting, everolimus-eluting and sirolimus-eluting stents used in our study may be superior to paclitaxel-eluting stents used in the SYNTAX substudy [34-42]. In addition, IVUS guided-PCI may be associated with a decreased rate of TVR [32, 43-45], and we had performed IVUS guided-PCI in some patients with high-risk lesions in this study.

Stroke is a well-known and serious complication in patients with CABG surgery, and it is usually procedure-related [7, 46]. A lot of studies such as the SYNTAX substudy and a meta-analysis of 24 studies showed that PCI with DES was associated with a lower incidence of stroke as compared with CABG in patients with ULMCA disease [20]. In spite of the incidence of stroke in our study trended to be lower in the PCI group as compared with that in the CABG group, this difference between the two groups was not statistically significant in the adjusted analysis. A similar result was obtained in the PRECOMBAT study. The reasons for this result may be due to low incidence of stroke, limited sample size and different ethnicities [9].

With regard to the incidence of death, a few observational studies indicated that PCI with DES was associated with significantly lower or a trend toward lower risk of death in patients with ULMCA disease [29, 47-49]. Similarly, in our study, death also occurred less frequently after PCI with DES than after CABG in the unadjusted analysis. However, most studies showed a similar incidence of death between the PCI and CABG groups [2, 7, 20], and the incidence of death in this study also had no significant difference between the two groups in our PS adjusted or matched analysis. A meta-analysis of 3 randomized trials and 9 observational studies has indicated that the average relative risk of death for PCI with DES versus CABG was lower in nonrandomized studies than in randomized trials [19], which suggest that selective bias may be the main reason for the lower risk of death in the PCI group in the observational studies.

SYNTAX score is very important for the evaluation of the severity of coronary lesions and the procedural risk. In the SYNTAX substudy, PCI patients with higher baseline SYNTAX scores (≥33) were associated with significantly worse outcomes, but baseline SYNTAX scores had no significant correlations with the outcomes of patients treated with CABG. The above finding has been supported by some other studies, and calculation of SYNTAX score has been recommended by current guidelines to guide the selection of treatment strategy for ULMCA disease [3, 4, 50]. However, our study indicated that the incidence of MACCE was no significant difference between the PCI and CABG groups in patients with high baseline SYNTAX scores (≥33). A result consistent with our above finding was reported in the PRECOMBAT study. The reasons for the above inconsistent results are unclear, but may be multifactorial. To begin with, the SYNTAX score only focuses on anatomical characteristic, and clinical factors are neglected. Recent studies have shown that combining anatomical and clinical factors were more appropriate to evaluate the procedural risk of patients [51-53]. Furthermore, improved DES quality and stenting techniques, and advanced devices such as IVUS and IABP were used in the PCI group in our study, so the trend in favor of CABG was weakened. Last but not least, the severity of ULMCA true bifurcation lesions may be overestimated by the calculation of SYNTAX score.

Study limitations

There were several limitations in our study. Firstly, this was an observational study, so we used PS adjustment and matching to compensate the treatment selection bias. Secondly, the sample size of this single-center study was restricted due to the low incidence of ULMCA true bifurcation lesions, therefore, it was underpowered to compare the individual components of MACCE or ST/GO between the PCI and CABG groups, especially in the propensity-matched population, and the power of subgroups analysis was also limited. Thirdly, 1-year follow-up was inadequate to compare the treatment outcomes after PCI with DES versus CABG. Finally, dual antiplatelet therapy was not mandatory in patients treated with CABG, and so the clinical outcomes of the two groups may be influenced by the inconsistent pharmaceutical treatments.

Conclusions

We performed an observational cohort study to compare the 1-year clinical outcomes between PCI and CABG groups in patients with ULMCA true bifurcation lesions. Our findings highlight that PCI with DES was an effective and safe treatment strategy with similar clinical outcomes to CABG. However, considering the limitations of our study, the results of our study should be interpreted with caution, and further study should be performed to confirm our findings.

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Disclosure of conflict of interest

None.

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